```
### Status: Path 1 of [Dialog Information Services via Modem]

### Status: Initializing TCP/IP using (UseTelnetProto 1 ServiceID pto-dialog)
Trying 3106900061...Open

DIALOG INFORMATION SERVICES
PLEASE LOGON:
 ******** HHHHHHHH SSSSSSSS?
### Status: Signing onto Dialog
 ********
ENTER PASSWORD:
 ******** HHHHHHHH SSSSSSSS? ********
Welcome to DIALOG
### Status: Connected


Dialog level 01.07.09D

Last logoff:  12aug01 10:27:56
Logon file001 16aug01 07:15:19
           *** ANNOUNCEMENT ***
                    ***
--Important Notice to Freelance Authors--
See HELP FREELANCE for more information
                    ***
NEW FILE RELEASED
***EIU Business Magazines (File 622)
***IBISWorld Market Research (File 753)
***Investext PDF Index (File 745)
***Daily and Sunday Telegraph (London) Papers (File 756)
***The Mirror Group Publications (United Kingdom) (File 757)

UPDATING RESUMED
***Delphes European Business (File 481)
***Books In Print (File 470)
                           ***
RELOADED
***Kompass Middle East/Africa/Mediterranean (File 585)
***Kompass Asia/Pacific (File 592)
***Kompass Central/Eastern Europe (File 593)
***Kompass Canada (File 594)
***CANCERLIT (File 159)
***Information Science Abstracts (File 202)

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     >>>    of new databases, price changes, etc.      <<<
                    ****
KWIC is set to 50.
HILIGHT set on as '*'
 *                                  *

File   1:ERIC  1966-2001/Aug 06
       (c) format only 2001 The Dialog Corporation

      Set  Items  Description
      ---  -----  -----------
?b 155, 159, 5, 73
```

```
      16aug01 07:15:35 User259876 Session D250.1
           $0.24    0.069 DialUnits File1
     $0.24  Estimated cost File1
     $0.01  TYMNET
     $0.25  Estimated cost this search
     $0.25  Estimated total session cost   0.069 DialUnits


SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R)  1966-2001/Sep W2
  File 159:Cancerlit  1975-2001/Jul
        (c) format only 2001 Dialog Corporation
*File 159: This file has been reloaded. Accession Numbers have changed.
  File   5:Biosis Previews(R)  1969-2001/Aug W2
        (c) 2001 BIOSIS
  File  73:EMBASE  1974-2001/Aug W1
        (c) 2001 Elsevier Science B.V.
*File  73: For information about Explode feature please
see Help News73.

      Set  Items  Description
      ---  -----  -----------
?s (FPGS or (Folylpolyglutamyl (w) synthetase))
            586  FPGS
             54  FOLYLPOLYGLUTAMYL
          87828  SYNTHETASE
             41  FOLYLPOLYGLUTAMYL(W)SYNTHETASE
      S1     609  (FPGS OR (FOLYLPOLYGLUTAMYL (W) SYNTHETASE))
?s s1 and review
            609  S1
        1223505  REVIEW
      S2      13  S1 AND REVIEW
?rd
...completed examining records
      S3      11  RD (unique items)
?t s3/3,k/all

 3/3,K/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08996295   96328552   PMID: 8740793
 Critical factors for optimizing the 5-fluorouracil-folinic acid
association in cancer chemotherapy.
  Etienne MC; Guillot T; Milano G
  Centre Antoine Lacassagne, Nice, France.
  Annals of oncology (NETHERLANDS)  Mar 1996, 7 (3)  p283-9, ISSN
0923-7534  Journal Code: AYF
  Languages: ENGLISH
  Document type: Journal Article; Review; Review, Tutorial
  Record type: Completed

  ... the optimal FU-FA schedule and dose. In addition, it would be of
interest to identify FU-FA-responsive tumors. DESIGN: Our purpose was to
*review* preclinical and clinical data dealing with prediction of FU-FA
sensitivity and optimization of FU-FA schedules. RESULTS: Preclinical
studies have highlighted the importance of...

... FA responsiveness has been clearly demonstrated in patients with
colorectal and gastric cancers. Preliminary in vitro and clinical data have
shown that the folylpolyglutamate synthetase (*FPGS* ), the enzyme
responsible for folate polyglutamylation, is another promising tool for
identifying FU-FA-responsive tumors. So far, results of clinical trials do
not form...

... index of FU-FA chemotherapy. Finally, future clinical studies should
investigate tumoral parameters pharmacologically linked to FU-FA
```

sensitivity such as pre-treatment TS and *FPGS* activities. Such tumoral investigations along with FU and FA pharmacokinetic investigations should provide a better understanding of inter-patient variability in response to FU-FA...

3/3,K/2 (Item 1 from file: 159)
DIALOG(R)File 159:Cancerlit
(c) format only 2001 Dialog Corporation. All rts. reserv.

00915388 92677939
DEVELOPMENT OF NOVEL 5-HALOGENATED QUINAZOLINE ANALOGUES OF FOLIC ACID.
Fetzer OS
Medical Univ. of South Carolina
Diss Abstr Int [B]; 52 (2) 1991 ISSN 0419-4217
Languages: ENGLISH
Document Type: THESIS
Record type: Completed

...procedures. The six analogs of 5,8-dideazaisofolic acid, were designed as specific inhibitors of thymidylate synthase (TS) and as efficient substrates of folylpolyglutamate synthetase (*FPGS*), in order to allow the evaluation of the effects of 5-halogenation, 2-methylation, and N9-methylation on enzyme activity. Analogs of N(alpha)-(5,8-dideazaisoptero yl)-L-ornithine, were developed as reversed bridge inhibitors of *FPGS*. These analogs were designed to assess the effect of fluorination or chlorination at position 5 as well as methylation at position 2 on *FPGS* inhibition. A brief overview of antifolate cancer chemotherapy and a summary of folate metabolism provides the background for the development of these analogs. A *review* of inhibitors of the target enzymes TS and *FPGS* leads into the discussion of the design of the new analogs. The chemistry *review* emphasizes pertinent earlier work and is followed by a discussion of each of the reactions employed. The formation of the quinazoline nucleus, the lability of...

... magnetic resonance spectroscopy and mass spectroscopy are covered in depth. From the preliminary biological data of the analogs as substrates or inhibitors of hog liver *FPGS*, it appears that the substrate activities of 5,8-dideazaisofolates correlate with the inhibitory potencies of the corresponding L-ornithine analogs; the introduction of the 5-fluoro group enhances *FPGS* substrate activity significantly, although not as much as 5-chlorination; replacement of a 2-amino group by 2-methyl increases binding to *FPGS*; and N9-methylation does not enhance *FPGS* substrate activities for the compounds tested. (Full text available from University Microfilms International, Ann Arbor, MI, as Order No. AAD91-21284).

3/3,K/3 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2001 Elsevier Science B.V. All rts. reserv.

07686123 EMBASE No: 1999164961
Roles of folylpoly-gamma-glutamate synthetase in therapeutics with tetrahydrofolate antimetabolites: An overview
Moran R.G.
Dr. R.G. Moran, Massey Cancer Center, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298-0230 United States
Seminars in Oncology (SEMIN. ONCOL.) (United States) 1999, 26/2 SUUPL. (24-32)
CODEN: SOLGA ISSN: 0093-7754
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 50

Folylpoly-gamma-glutamate synthetase (*FPGS*) catalyzes the addition of several equivalents of glutamic acid to the gamma-carboxyl group in the

side chain of folate cofactors and analogs. Folylpoly-gamma...

...synthesis. The efficient substrate activity of the newer generations of tetrahydrofolate analogs results in levels of intracellular accumulation of cytotoxic drug in any cell expressing *FPGS* in which the enzyme activity is not suppressed by feedback, and the binding of folate inhibitors of thymidylate synthase and glycinamide ribonucleotide formyltransferase is substantially...

...cytotoxicity of both thymidylate synthase and purine inhibitors requires continued inhibition of target for greater than one generation time, so that the integrative function of *FPGS* adds considerably to the efficiency of folate antimetabolites.
MEDICAL DESCRIPTORS:
drug resistance; drug structure; tumor cell line; mutation; human; nonhuman ; *review*; priority journal

3/3,K/4 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2001 Elsevier Science B.V. All rts. reserv.

07382439 EMBASE No: 1998294610
Nonpolyglutamatable antifolates as inhibitors of thymidylate synthase (TS) and potential antitumour agents
Bavetsias V.; Jackman A.L.
V. Bavetsias, CRC, Centre for Cancer Therapeutics, Institute of Cancer Research, CRC Laboratory, 15 Cotswold Road, Sutton, Surrey SM2 5NG United Kingdom
Current Medicinal Chemistry (CURR. MED. CHEM.) (Netherlands) 1998, 5/4 (265-288)
CODEN: CMCHE ISSN: 0929-8673
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 74

...devoted to the design and development of nonpolyglutamatable inhibitors of TS as antitumour agents, mainly to overcome resistance due to unfavourable expression of folylpolyglutamate synthetase (*FPGS*). Lipophilic inhibitors of the enzyme were expected not to depend on the reduced folate carrier transporter (RFC) for cellular uptake, thus avoiding resistance due to...
MEDICAL DESCRIPTORS:
...inhibition; drug metabolism; lipophilicity; structure activity relation; cytotoxicity; drug uptake; cell line; cell growth; leukemia l 1210; human; nonhuman; controlled study; human cell; animal cell; *review*

3/3,K/5 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2001 Elsevier Science B.V. All rts. reserv.

06763214 EMBASE No: 1997044705
Folate-based thymidylate synthase inhibitors in cancer chemotherapy
Takemura Y.; Jackman A.L.
Y. Takemura, Department of Laboratory Medicine, National Defense Medical College, 3-2 Namiki, Tokorozawa, Saitama 359 Japan
Anti-Cancer Drugs (ANTI-CANCER DRUGS) (United Kingdom) 1997, 8/1 (3-16)
CODEN: ANTDE ISSN: 0959-4973
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 115

...relationship between chemical structure and biological properties of folate analogs, particularly their interactions with the target enzymes,

transport proteins and folate-metabolizing enzyme, folylpolyglutamate synthetase (*FPGS*), has enabled the rational design and development of the selective thymidylate synthase (TS) inhibitors with folate-based structures for clinical uses. These compounds specifically inhibit...

...than seen with the latter regimen. The newer selective TS inhibitors, which retain potency for TS inhibition but are not substrates for RFC and/or *FPGS*, are currently under clinical evaluation. These classes of compound may have benefits for circumvention of resistance by virtue of alterations in these protein functions and...
MEDICAL DESCRIPTORS:
clinical trial; colorectal cancer--drug therapy--dt; human; mouse; nonhuman ; priority journal; rat; *review*; structure activity relation

3/3,K/6 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2001 Elsevier Science B.V. All rts. reserv.

06684448 EMBASE No: 1996349366
Exploitation of folate and antifolate polyglutamylation to achieve selective anticancer chemotherapy
McGuire J.J.; Tsukamoto T.; Hart B.P.; Coward J.K.; Kalman T.I.; Galivan J.
Grace Cancer Drug Center, Roswell Park Cancer Institute, Elm and Carlton Streets,Buffalo, NY 14263 United States
Investigational New Drugs (INVEST. NEW DRUGS) (United States) 1996, 14/3 (317-323)
CODEN: INNDD ISSN: 0167-6997
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

...Inhibition of folylpolyglutamate synthesis should lead to cell death. Current ornithine (Orn)-containing folate-based inhibitors of the enzyme responsible for their synthesis, folylpolyglutamate synthetase (*FPGS*), are poorly transported, apparently because of interference by the protonated delta-amine. Replacement of Orn with 4,4-difluoroOrn, the delta-amine of which has...

...antifolate by some Glu analogs in which the gamma-COOH is either altered or replaced (e.g., gamma-tetrazole-Glu) leads to loss of both *FPGS* substrate activity and binding; antifolate target specificity is unchanged, while uptake is actually enhanced. Substitution of 3,3-difluoroGlu for Glu leads to enhanced polyglutamylation...
MEDICAL DESCRIPTORS:
cancer chemotherapy; cell death; cytotoxicity; drug synthesis; metabolism; ph; priority journal; *review*

3/3,K/7 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2001 Elsevier Science B.V. All rts. reserv.

06684447 EMBASE No: 1996349365
Tomudex(R) (ZD1694): From concept to care, a programme in rational drug discovery
Jackman A.L.; Boyle F.T.; Harrap K.R.
CRC Centre for Cancer Therapeutics, Institute of Cancer Research, Cotswold Road,Sutton SM2 5NG United Kingdom
Investigational New Drugs (INVEST. NEW DRUGS) (United States) 1996, 14/3 (305-316)
CODEN: INNDD ISSN: 0167-6997
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

...belongs to a class of compounds that use the reduced-folate carrier

(RFC) for uptake into cells and which are excellent substrates for folylpolyglutamate synthetase (*FPGS*). This paper reviews the underlying philosophies, and the milestones reached during the development of Tomudex.
MEDICAL DESCRIPTORS:
colorectal cancer--drug therapy--dt; drug solubility; enzyme inhibition; nephrotoxicity--etiology--et; priority journal; *review*

3/3,K/8 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2001 Elsevier Science B.V. All rts. reserv.

06401951 EMBASE No: 1996063425
Role of folylpolyglutamate synthetase (*FPGS*) in antifolate chemotherapy; A biochemical and clinical update
Synold T.W.; Willits E.M.; Barredo J.C.
Pediatric Hematology-Oncology, MUSC Children's Hospital, 171 Ashley Ave.,Charleston, SC 29425 United States
Leukemia and Lymphoma (LEUK. LYMPHOMA) (United Kingdom) 1996, 21/1-2 (9-15)
CODEN: LELYE ISSN: 1042-8194
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Role of folylpolyglutamate synthetase (*FPGS*) in antifolate chemotherapy; A biochemical and clinical update
MEDICAL DESCRIPTORS:
acute lymphoblastic leukemia--drug therapy--dt; cancer--drug therapy--dt; drug activation; drug safety; human; metabolism; nonhuman; priority journal ; purine synthesis; *review*

3/3,K/9 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2001 Elsevier Science B.V. All rts. reserv.

06323699 EMBASE No: 1995351591
Folate-based thymidylate synthase inhibitors as anticancer drugs
Jackman A.L.; Calvert A.H.
CRC Centre for Cancer Therapeutics, Institute of Cancer Research, 15 Cotswold Road,Sutton, Surrey SM2 5NG United Kingdom
Annals of Oncology (ANN. ONCOL.) (Netherlands) 1995, 6/9 (871-881)
CODEN: ANONE ISSN: 0923-7534
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

...were developed with an interesting diversity in biochemical profile, particularly with respect to interactions with the reduced-folate cell membrane carrier (RFC) and folylpolyglutamate synthetase (*FPGS*). An example of a compound that uses both of these processes well is the quinazoline, ZD1694 (Tomudex), a drug which is about to complete phase...

...which has somewhat different properties. It is a very potent TS inhibitor (Ki = 0.09 nM) and an excellent substrate for the RFC (human) and *FPGS*, but polyglutamation proceeds to diglutamate only and is not accompanied by increased TS inhibition. Another highly water-soluble compound in pre-clinical development is ZD9331 which was specifically designed to use the RFC but not be a substrate for *FPGS*. Potent TS inhibition (Ki = 0.4 nM) was achieved through a rational programme of computerised molecular modelling of the active site of TS and a large database of structure-activity relationships. Two lipophilic compounds were designed to be devoid of interactions with either the RFC or *FPGS*. High resolution crystal complexes of E. coli TS were central to obtaining potent TS inhibitors and both AG337 (Ki human recombinant TS = 16 nM) and...
MEDICAL DESCRIPTORS:
clinical trial; human; nephrotoxicity; nonhuman; priority journal; *review*

3/3,K/10 (Item 8 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2001 Elsevier Science B.V. All rts. reserv.

04594308 EMBASE No: 1991088351
Folate analogues. 34. Synthesis and antitumor activity of non-polyglutamylatable inhibitors of dihydrofolate reductase
Abraham A.; McGuire J.J.; Galivan J.; Nimec Z.; Kisliuk R.L.; Gaumont Y.; Nair M.G.
Drug Development Laboratory, Cancer Center, Department of Biochemistry,Mobile, AL 36688 United States
Journal of Medicinal Chemistry (J. MED. CHEM.) (United States) 1991, 34/1 (222-227)
CODEN: JMCMA ISSN: 0022-2623
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

...compounds were metabolized to the respective polyglutamate derivative as judged by their inability to serve as substrates for CCRF-CEM human leukemia cell folylpolyglutamate synthetase (*FPGS*) in vitro. All compounds inhibited recombinant human-dihydrofolate reductase (DHFR) at nearly equivalent magnitude as MTX. Growth inhibition studies with H35 hepatoma, Manca human lymphoma...
MEDICAL DESCRIPTORS:
animal cell; drug metabolism; enzyme activity; enzyme inhibition; human; human cell; leukemia cell; liver cell carcinoma; lymphoma; nonhuman; priority journal; *review*

3/3,K/11 (Item 9 from file: 73)
DIALOG(R)File 73:EMBASE
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03784960 EMBASE No: 1988234400
Insulin: either alone or combined with oral hypoglycemic agents
Firth R.G.
Mater Misericordiae Hospital, Dublin 7 Ireland
Primary Care - Clinics in Office Practice (PRIM. CARE CLIN. OFF. PRACT.) (United States) 1988, 15/3 (665-683)
CODEN: PRCAD ISSN: 0095-4543
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

...insulin deficiency and insulin resistance that lead to hepatic glucose over-production and diminished glucose tissue utilization. Both sulfonylureas and insulin can achieve near normal *FPGs* and HbA(1c) concentrations in mild to moderately severe NIDDM. Both can reduce insulin resistance and both increase insulin availability. Evidence exists, however, showing that...
MEDICAL DESCRIPTORS:
adult; age; aged; *review*; human; oral drug administration; subcutaneous drug administration
?ds

Set	Items	Description
S1	609	(FPGS OR (FOLYLPOLYGLUTAMYL (W) SYNTHETASE))
S2	13	S1 AND REVIEW
S3	11	RD (unique items)

?s s1 and (gene or cDNA or DNA)

	609	S1
	1856966	GENE
	246255	CDNA
	1860027	DNA
S4	195	S1 AND (GENE OR CDNA OR DNA)

```
?s s4 and review
             195  S4
         1223505  REVIEW
      S5       1  S4 AND REVIEW
?t s5/3,k/all
```

5/3,K/1 (Item 1 from file: 73)

```
DIALOG(R)File  73:EMBASE
(c) 2001 Elsevier Science B.V. All rts. reserv.

06401951     EMBASE No: 1996063425
```

Role of folylpolyglutamate synthetase (*FPGS*) in antifolate chemotherapy; A biochemical and clinical update

Synold T.W.; Willits E.M.; Barredo J.C.
Pediatric Hematology-Oncology, MUSC Children's Hospital, 171 Ashley Ave., Charleston, SC 29425 United States

Leukemia and Lymphoma (LEUK. LYMPHOMA) (United Kingdom) 1996, 21/1-2 (9-15)
CODEN: LELYE ISSN: 1042-8194
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Role of folylpolyglutamate synthetase (*FPGS*) in antifolate chemotherapy; A biochemical and clinical update

```
DRUG DESCRIPTORS:
alkylating agent--drug therapy--dt; *dna* topoisomerase--endogenous
compound--ec; enzyme inhibitor--drug therapy--dt; fluorouracil--drug
therapy--dt; fluorouracil--drug combination--cb; folinic acid--drug therapy
--dt; folinic acid--drug...
MEDICAL DESCRIPTORS:
acute lymphoblastic leukemia--drug therapy--dt; cancer--drug therapy--dt;
drug activation; drug safety; human; metabolism; nonhuman; priority journal
; purine synthesis; *review*
CAS REGISTRY NO.: 63363-84-8 (folylpolyglutamate synthase); 80449-01-0 (
    *dna* topoisomerase); 51-21-8 (fluorouracil); 58-05-9...
?ds

Set     Items   Description
S1        609   (FPGS OR (FOLYLPOLYGLUTAMYL (W) SYNTHETASE))
S2         13   S1 AND REVIEW
S3         11   RD (unique items)
S4        195   S1 AND (GENE OR CDNA OR DNA)
S5          1   S4 AND REVIEW
?s s4 and (mammal or animal)
             195  S4
          119081  MAMMAL
         5899114  ANIMAL
      S6      61  S4 AND (MAMMAL OR ANIMAL)
?rd
...examined 50 records  (50)
...completed examining records
      S7      35  RD (unique items)
?s s7/3,k/1-10
>>>Invalid syntax
?t s7/3,k/1-10
```

7/3,K/1 (Item 1 from file: 155)

```
DIALOG(R)File 155:MEDLINE(R)

11461090   21126588   PMID: 11223131
```

A bifunctional dihydrofolate synthetase--folylpolyglutamate synthetase in Plasmodium falciparum identified by functional complementation in yeast and bacteria.

Salcedo E; Cortese JF; Plowe CV; Sims PF; Hyde JE
Department of Biomolecular Sciences, University of Manchester Institute of Science and Technology, PO Box 88, Manchester M60 1QD, UK.

Molecular and biochemical parasitology (Netherlands) Feb 2001, 112 (2) p239-52, ISSN 0166-6851 Journal Code: NOR
Contract/Grant No.: R01-AI44824, AI, NIAID
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

... mutants of both Escherichia coli and Saccharomyces cerevisiae, we demonstrate here that one of these parasite genes encodes both dihydrofolate synthetase (DHFS) and folylpolyglutamate synthetase (*FPGS*) activities, which catalyse the synthesis and polyglutamation of folate derivatives, respectively. The malaria parasite is the first known example of a eukaryote encoding both DHFS and *FPGS* activities in a single *gene*. *DNA* sequencing of this *gene* in antifolate-resistant strains of P. falciparum, as well as drug-inhibition assays performed on yeast and bacteria expressing PfDHFS--*FPGS* , indicate that current antifolate regimes do not target this enzyme. As PfDHFS--*FPGS* harbours two activities critical to folate metabolism, one of which has no human counterpart, this *gene* product offers a novel chemotherapeutic target with the potential to deliver a powerful blockage to parasite growth.

Tags: *Animal*;

; Amino Acid Sequence; Base Sequence; Cloning, Molecular; Escherichia coli--enzymology--EN; Escherichia coli--metabolism--ME; Folic Acid Antagonists--pharmacology--PD; *Gene* Deletion; Genes, Protozoan--genetics --GE; Genetic Complementation Test; Glycine--metabolism--ME; Methionine --metabolism--ME; Molecular Sequence Data; Multienzyme Complexes--chemistry --CH; Multienzyme Complexes--genetics--GE...

7/3,K/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11175758 21039482 PMID: 11197757
Characterization of three genes encoding enzymes of the folate biosynthetic pathway in Plasmodium falciparum.

Lee CS; Salcedo E; Wang Q; Wang P; Sims PF; Hyde JE
Department of Biomolecular Sciences, University of Manchester Institute of Science and Technology (UMIST), UK.

Parasitology (England) Jan 2001, 122 Pt 1 p1-13, ISSN 0031-1820 Journal Code: ORO
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

... pathway, we report the isolation and characterization of 3 new genes that encode homologues of GTP cyclohydrolase I (GTP-CH), dihydrofolate synthase/folylpolyglutamate synthase (DHFS/*FPGS*) and serine hydroxymethyltransferase (SHMT). The genes encoding GTP-CH and SHMT are unambiguously assigned to chromosome 12, while that for DHFS/*FPGS* is tentatively assigned to chromosome 13. All 3 genes are expressed in blood-stage parasites, yielding transcripts of which only ca 60-70% is accounted...
... that may be of functional significance. These data bring the complement of cloned genes that encode activities in the pathway to seven, leaving only the *gene* encoding dihydroneopterin aldolase (DHNA) to be identified in the route from GTP to folate synthesis and folate turnover in the thymidylate cycle.

Tags: *Animal*;

; Aldehyde-Lyases--genetics--GE; Amino Acid Sequence; Caenorhabditis elegans; Chromosomes; Cloning, Molecular; Escherichia coli; *Gene* Expression Regulation, Enzymologic; Guanosine Triphosphate--metabolism--ME ; Molecular Sequence Data; Saccharomyces cerevisiae; Sequence Alignment; Sequence Homology, Amino Acid; Sequence Homology, Nucleic Acid

7/3,K/3 (Item 3 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

10898670 20549604 PMID: 10964921
Expression patterns of the multiple transcripts from the folylpolyglutamate synthetase *gene* in human leukemias and normal differentiated tissues.
Turner FB; Taylor SM; Moran RG
Departments of Pharmacology and Toxicology, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23298, USA.
Journal of biological chemistry (UNITED STATES) Nov 17 2000, 275 (46) p35960-8, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: CA-39687, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Expression patterns of the multiple transcripts from the folylpolyglutamate synthetase *gene* in human leukemias and normal differentiated tissues.
Folylpoly-gamma-glutamate synthetase (*FPGS*) catalyzes the activation of folate antimetabolites in mammalian tissues and tumors. We have determined the sequence, abundance, and function of human *FPGS* transcripts and found some striking differences to transcription of the mouse *gene* that allow production of *FPGS* isoforms in mouse liver and dividing tissues. Multiple human transcripts were identified, including the homolog of the mouse transcripts that initiate at two upstream exons. However, the human *FPGS* upstream promoter is infrequently used, and transcripts from this promoter include sequences homologous with only one of the upstream exons found in the mouse. The...

...of transcripts, some of which do not produce active enzyme, a phenomenon not seen in the mouse. Hence, the dual promoter mechanism directing expression of *FPGS* isozymes in mouse tissues is not conserved in humans, and, unlike the mouse downstream promoter, the human downstream promoter is active in both dividing and differentiated tissues. This study raises questions about the differences in function served by the two mouse *FPGS* isozymes and how, or if, human tissues fulfill these functions. How humans and mice produce *FPGS* in only a subset of tissues using such different promoter structures also becomes a central issue.
Tags: *Animal*;
Descriptors: *Gene* Expression Regulation, Enzymologic; **Gene* Expression Regulation, Neoplastic; *Leukemia--enzymology--EN; *Peptide Synthases--genetics--GE

7/3,K/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10806665 99341974 PMID: 10413425
***Folylpolyglutamyl* *synthetase* *gene* transfer and glioma antifolate sensitivity in culture and in vivo.**
Aghi M; Kramm CM; Breakefield XO
Department of Neurology, Massachusetts General Hospital, Boston, MA, USA.
Journal of the National Cancer Institute (UNITED STATES) Jul 21 1999, 91 (14) p1233-41, ISSN 0027-8874 Journal Code: J9J
Contract/Grant No.: P30CA69246, CA, NCI
Comment in J Natl Cancer Inst. 1999 Dec 1;91(23) 2047-50; Comment in J Natl Cancer Inst. 1999 Jul 21;91(14):1178-9
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

***Folylpolyglutamyl* *synthetase* *gene* transfer and glioma antifolate sensitivity in culture and in vivo.**
... against slow-growing tumors and are toxic to actively replicating cells in normal tissues. These drugs are converted intracellularly into

polyglutamate derivatives by the enzyme *folylpolyglutamyl* *synthetase* (*FPGS*). Because tumors with high expression of *FPGS* often respond to nontoxic antifolate doses, we investigated whether augmenting tumoral *FPGS* activity by *gene* delivery would enhance tumoral antifolate sensitivity. METHODS: 9L rat gliosarcoma cells were stably transfected with a human *FPGS* complementary *DNA* (*cDNA*), producing 9L/*FPGS* cells. The sensitivity of these cells to the antifolates methotrexate and edatrexate was measured in culture and in subcutaneous tumors, as was their ability to ...

... the chemosensitivity of nearby nontransfected cells, i.e., a bystander effect. The antifolate sensitivity of nonselected cells transduced with a hybrid amplicon vector that expressed *FPGS* was also ascertained. RESULTS: In comparison with 9L cells, 9L/*FPGS* cells displayed enhanced sensitivity to 4-hour pulses of antifolate. Subcutaneous 9L/*FPGS* tumors responded as well to methotrexate given every third day as 9L tumors did to daily treatment. A modest bystander effect was observed with edatrexate...

...drug. In culture, enhanced antifolate sensitivity was also seen in other stably transfected rodent and human glioma cell lines, including one with high pre-existing *FPGS* activity, and in canine and human glioblastoma cell lines transduced with a vector bearing *FPGS* *cDNA*. CONCLUSIONS: *FPGS* *gene* delivery enhances the antifolate sensitivity of several glioma cell lines and merits further evaluation as a therapeutic strategy.
Tags: *Animal*;
Descriptors: Aminopterin--analogs and derivatives--AA; *Antimetabolites, Antineoplastic--pharmacology--PD; *Folic Acid Antagonists--pharmacology--PD ; **Gene* Therapy--methods--MT; **Gene* Transfer Techniques; *Methotrexate --pharmacology--PD; *Neoplasms--therapy--TH; *Peptide Synthases--genetics --GE

7/3,K/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10770844 20048020 PMID: 10580033
Re: *Folylpolyglutamyl* *synthetase* *gene* transfer and glioma antifolate sensitivity in culture and in vivo.
Jansen G; Peters GJ; Pinedo HM; Priest DG; Assaraf YG
Journal of the National Cancer Institute (UNITED STATES) Dec 1 1999, 91 (23) p2047-50, ISSN 0027-8874 Journal Code: J9J
Comment on J Natl Cancer Inst. 1999 Jul 21;91(14) 1178-9; Comment on J Natl Cancer Inst. 1999 Jul 21;91(14):1233-41
Languages: ENGLISH
Document type: Comment; Letter
Record type: Completed

Re: *Folylpolyglutamyl* *synthetase* *gene* transfer and glioma antifolate sensitivity in culture and in vivo.
Tags: *Animal*;
Descriptors: Antimetabolites, Antineoplastic--therapeutic use--TU; *Enzyme Inhibitors--therapeutic use--TU; *Folic Acid Antagonists --therapeutic use--TU; **Gene* Therapy; *Glioma--therapy--TH; *Peptide Synthases--genetics--GE; *Gene* Transfer Techniques; Glioma--enzymology--EN ; Tumor Cells, Cultured

7/3,K/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10733489 20409018 PMID: 10856298
Molecular analysis of murine leukemia cell lines resistant to 5, 10-dideazatetrahydrofolate identifies several amino acids critical to the function of folylpolyglutamate synthetase.
Zhao R; Titus S; Gao F; Moran RG; Goldman ID
Albert Einstein College of Medicine, Comprehensive Cancer Center, Bronx,

New York 10461, USA.
Journal of biological chemistry (UNITED STATES) Aug 25 2000, 275 (34) p26599-606, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: CA-39687, CA, NCI; CA-39807, CA, NCI; CA-82621, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

... DDATHF and ALIMTA (LY231514, MTA) were markedly decreased in these mutant cell lines. Membrane transport was not a factor in drug resistance; rather, folypolyglutamate synthetase (*FPGS*) activity was decreased by >98%. In each cell line, *FPGS* mRNA expression was unchanged but both alleles of the *FPGS* *gene* bore a point mutation in highly conserved domains of the coding region. Four mutations were in the predicted ATP-, folate-, and/or glutamate-binding sites of *FPGS*, and two others were clustered in a peptide predicted to be beta sheet 5, based on the crystal structure of the Lactobacillus casei enzyme. Transfection of cDNAs for three mutant enzymes into *FPGS*-null Chinese hamster ovary cells restored a reduced level of clonal growth, whereas a T339I mutant supported growth at a level comparable to that of...

...one in the loop between NH(2)- and COOH-terminal domains did not support cell growth. When sets of mutated cDNAs were co-transfected into *FPGS* -null cells to mimic the genotype of drug-selected resistant cells, clonal growth was restored. These results demonstrate for the first time that single amino acid substitutions in several critical regions of *FPGS* can cause marked resistance to tetrahydrofolate antimetabolites, while still allowing cell survival.
Tags: *Animal*;

7/3,K/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10534042 20184744 PMID: 10721719
Two promoters regulate transcription of the mouse folylpolyglutamate synthetase *gene* three tightly clustered Sp1 sites within the first intron markedly enhance activity of promoter B.
Chen J; Hayes P; Roy K; Sirotnak FM
Program of Molecular Pharmacology and Experimental Therapeutics, Memorial Sloan-Kettering Cancer Center, Cornell University, New York, NY 10021, USA.
Gene (NETHERLANDS) Jan 25 2000, 242 (1-2) p257-64, ISSN 0378-1119 Journal Code: FOP
Contract/Grant No.: CA08748, CA, NCI; CA55617, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Two promoters regulate transcription of the mouse folylpolyglutamate synthetase *gene* three tightly clustered Sp1 sites within the first intron markedly enhance activity of promoter B.
The process of polyglutamylation mediated by folylpolyglutamate synthetase (*FPGS*) in mammalian cells has nutritional and pharmacological importance. In murine cells, *FPGS* expression is controlled by two promoters that, as we show here, vary substantially in their efficiency, at least in the context of a reporter *gene* assay. Characteristics of the most efficient promoter (promoter B) were examined in the present studies. Insertion in pGL3 of a 1635 bp segment of upstream...

... exon B1a resulted in a 15-20-fold increase in transcription in NIH3T3 and Hep1-6 cells compared with the promoterless vector. Deletion analysis of *DNA* sequence upstream of exon B1c showed that transcription was regulated by putative cis active elements only within two distally located upstream segments which when deleted...

...of and within exon B1c as well as downstream in exon B1a. This result is consistent with the frequent occurrence in murine cells of an *FPGS* variant (variant III) incorporating exon B1c [Roy et al., J. Biol. Chem. 271 (1996) 23820; 272 (1997) 5587]. Site-directed mutagenesis and DNAse I footprinting...

...we demonstrate that Sp1 can induce high levels of promoter B activity in pGL3 transfectants, but only when intron B1c is included within the reporter *gene* construct used. These results suggest that the unusually tight cluster of active Sp1 sites within intron B1c are essential and sufficient for maximal activity of...

Tags: *Animal*;

; 3T3 Cells; Base Sequence; Binding Sites; Cell Line; *DNA* Footprinting; Deoxyribonuclease I--metabolism--ME; Enhancer Elements (Genetics)--genetics --GE; *Gene* Expression Regulation, Enzymologic; Genes, Reporter--genetics --GE; Mice; Molecular Sequence Data; Mutagenesis, Site-Directed; Peptide Synthases--metabolism--ME; Protein Binding; RNA, Messenger--genetics--GE; Recombinant...

7/3,K/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10498885 20115263 PMID: 10648167

Purification and characteristics of recombinant human folylpoly-gamma-glutamate synthetase expressed at high levels in insect cells.

Sanghani PC; Moran RG

Department of Pharmaceutical Sciences, University of Southern California, Los Angeles, California, 90033, USA.

Protein expression and purification (UNITED STATES) Feb 2000, 18 (1) p36-45, ISSN 1046-5928 Journal Code: BJV

Contract/Grant No.: CA-39687, CA, NCI

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

... very low levels of endogenous expression of this enzyme have greatly limited its study. We now report the expression of cytosolic folylpoly-gamma-glutamate synthetase (*FPGS*) cloned from human leukemic cells in baculovirus-infected insect cells at levels of 4-5% of the total soluble protein of the cells. As was the case with endogenously expressed mammalian *FPGS* , recombinant enzyme was quantitatively blocked at the amino terminus in spite of the large-scale production in insect cells. A three-step purification procedure resulted...

Tags: *Animal*;

; Adenosinetriphosphatase--metabolism--ME; Baculoviridae--genetics--GE; Cell Line; Cytosol--enzymology--EN; Enzyme Stability; *Gene* Expression; Kinetics; Peptide Synthases--metabolism--ME; Pteroylpolyglutamic Acids --biosynthesis--BI; Recombinant Proteins--genetics--GE; Recombinant Proteins--isolation and purification--IP; Recombinant Proteins--metabolism --ME; Spodoptera...

7/3,K/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10446806 20090219 PMID: 10626793

Tissue-specific expression of functional isoforms of mouse folypoly-gamma-glutamae synthetase: a basis for targeting folate antimetabolites.

Turner FB; Andreassi 2nd JL; Ferguson J; Titus S; Tse A; Taylor SM; Moran RG

Department of Pharmacology and Toxicology, Medical College of Virginia, Virginia Commonwealth University, Richmond 23298, USA.

Cancer research (UNITED STATES) Dec 15 1999, 59 (24) p6074-9, ISSN

0008-5472 Journal Code: CNF
Contract/Grant No.: CA-39687, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Folates and folate antimetabolites are metabolically trapped in mammalian cells as polyglutamates, a process catalyzed by folylpoly-gamma-glutamate synthetase (*FPGS*). Using 5'-rapid amplification of *cDNA* ends, RNase protection assays, transfection of cDNAs into *FPGS*-deficient cells, and kinetic analysis of recombinant enzymes expressed in insect cells, it was determined that the species of active *FPGS* in mouse liver and kidney was different from that in mouse tumor cells, bone marrow, and intestine. The NH2-terminal peptide of hepatic enzyme contained...

...one of two alternative sets of initial coding exons in different tissues underlies this phenomenon, suggesting the design of antifolates specific for activation by individual *FPGS* isoforms and hence tissue-selective targeting of antifolate therapy for cancer, arthritis, or psoriasis.
Tags: *Animal*;
; Amino Acid Sequence; Base Sequence; *DNA*, Complementary--isolation and purification--IP; Folic Acid Antagonists--metabolism--ME; Isoenzymes --chemistry--CH; Isoenzymes--genetics--GE; Kinetics; Leukemia L1210 --enzymology--EN; Mice; Molecular Sequence Data...
Chemical Name: *DNA*, Complementary; Folic Acid Antagonists; Isoenzymes; Recombinant Proteins; Peptide Synthases; folylpolyglutamate synthetase

7/3,K/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10380878 99399392 PMID: 10470377
Folylpoly-gamma-glutamate synthetase: generation of isozymes and the role in one carbon metabolism and antifolate cytotoxicity.
Qi H; Atkinson I; Xiao S; Choi YJ; Tobimatsu T; Shane B
Department of Nutritional Sciences, University of California, Berkeley 94720-3104, USA.
Advances in enzyme regulation (ENGLAND) 1999, 39 p263-73, ISSN 0065-2571 Journal Code: 2LG
Contract/Grant No.: CA41991, CA, NCI; DK42033, DK, NIDDK
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

A single human *gene* encodes both mitochondrial and cytosolic isoforms of the enzyme. The major mRNA species in human cells encodes the mitochondrial isoform but alternate translation initiation at a downstream in-frame ATG also generates the cytosolic isoform. Cytosolic *FPGS* may also be generated by use of alternate transcription initiation start sites 3' to the start ATG of the mitochondrial *FPGS*. Three additional human *FPGS* mRNAs differing in exon 1 have been identified. One of these is a major species in HEP-G2 cells and other tissue culture cells, and can encode a protein lacking the first 8 amino acids of cytosolic *FPGS*. A protein of the predicted size is observed in coupled transcription/translation systems. However, expression of this protein in E. coli does not generate an...

... Tyr-3 of the missing N terminal residues is required for enzyme activity. The major cellular folate pools are in the cytosol and mitochondria and *FPGS* activity is normally distributed in both compartments. Mitochondrial *FPGS* activity is required for mitochondrial folate accumulation, and cells lacking this isozyme are auxotrophic for glycine. Overexpression of cytosolic *FPGS* does not complement the lack of mitochondrial activity. Cells expressing *FPGS* activity solely in the mitochondria are glycine prototrophs, but also possess cytosolic folylpolyglutamates and are prototrophic for thymidine and purines,

products of cytosolic one carbon...

...mitochondrial folylpolyglutamates are released intact into the cytosolic compartment. Cellular accumulation of some antifolates and their cytotoxic efficacy is highly responsive to the level of *FPGS* activity. Polyglutamylation of methotrexate (MTX) has little affect on its affinity for dihydrofolate reductase, its target enzyme, but does affect the cellular accumulation of the drug. The sensitivity of model cells, expressing a range of *FPGS* activities similar to that observed in leukemia blasts, to MTX varied over four orders of magnitude. MTX toxicity was dependent on cytosolic *FPGS* activity as this drug does not enter the mitochondria, and cells expressing very high levels of *FPGS* solely in the mitochondria were resistant to MTX. The cytotoxic efficacy of other folate antagonists that are transported into the mitochondria was enhanced by mitochondrial *FPGS* activity, even when their loci of inhibition was a cytosolic enzyme. Mitochondrial metabolism of these drugs increased cytosolic drug levels. Compartmentalization of antifolate metabolism has...

Tags: *Animal*;
; Amino Acid Sequence; Base Sequence; CHO Cells; Cytosol--enzymology--EN; *DNA*, Complementary--genetics--GE; Escherichia coli--genetics--GE; Folic Acid--metabolism--ME; Folic Acid Antagonists--metabolism--ME; *Gene* Expression; Hamsters; Isoenzymes--genetics--GE; Methotrexate--metabolism --ME; Methotrexate--pharmacology--PD; Mitochondria--enzymology--EN; Molecular Sequence Data; Peptide Synthases--genetics--GE; Transfection

Chemical Name: *DNA*, Complementary; Folic Acid Antagonists; Isoenzymes; Methotrexate; Folic Acid; Peptide Synthases; folylpolyglutamate synthetase

?ds

Set	Items	Description
S1	609	(FPGS OR (FOLYLPOLYGLUTAMYL (W) SYNTHETASE))
S2	13	S1 AND REVIEW
S3	11	RD (unique items)
S4	195	S1 AND (GENE OR CDNA OR DNA)
S5	1	S4 AND REVIEW
S6	61	S4 AND (MAMMAL OR ANIMAL)
S7	35	RD (unique items)

?t s7/3,k/11-20

7/3,K/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09937110 98451712 PMID: 9778690
Folylpolyglutamate synthetase expression in antifolate-sensitive and -resistant human cell lines.
McGuire JJ; Russell CA
Grace Cancer Drug Center, Roswell Park Cancer Institute, Buffalo, NY 14263, USA.
Oncology research (UNITED STATES) 1998, 10 (4) p193-200, ISSN 0965-0407 Journal Code: BBN
Contract/Grant No.: CA16056, CA, NCI; CA43500, CA, NCI; CA65755, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Synthesis of poly(gamma-glutamyl) metabolites of many antifolates, such as methotrexate (MTX), by folylpolyglutamate synthetase (*FPGS*) is often essential to their cytotoxic activity. *FPGS* expression in the MTX-sensitive human T-lymphoblastic leukemia cell line CCRF-CEM and a number of MTX-resistant sublines was previously investigated at the *DNA*, RNA, and activity levels. Using an *FPGS* peptide deduced from its *cDNA* sequence, a rabbit polyclonal antibody to *FPGS* has now been elicited, immunoaffinity purified, and used to quantitate *FPGS* protein expression by chemiluminescent Western immunoblot analysis. The antibody was used to determine the half-life of human *FPGS* protein (3.7 +/- 1.1 h) in parental CCRF-CEM cells. A subline resistant to MTX as a result of amplified dihydrofolate reductase expression shows no change in *FPGS* protein or

activity relative to CCRF-CEM. An MTX transport-defective line, however, displays both higher *FPGS* protein and activity levels. For several sublines in which the only apparent mechanism of MTX resistance is decreased *FPGS* activity, the *FPGS* protein level is decreased proportionally. However, we previously showed that these sublines have the same *gene* copy number, restriction map, and mRNA size and levels as the parent. Evidently, in these MTX-resistant sublines the mRNA is poorly translated and/or...
Tags: *Animal*;

7/3,K/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09590646 97460138 PMID: 9312158
Transcription of the human folylpoly-gamma-glutamate synthetase *gene*.
Freemantle SJ; Moran RG
Department of Pharmacology and Toxicology and the Massey Cancer Center, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23298, USA.
Journal of biological chemistry (UNITED STATES) Oct 3 1997, 272 (40) p25373-9, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: CA 27605, CA, NCI; CA 39687, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Transcription of the human folylpoly-gamma-glutamate synthetase *gene*.
In mammals, folylpoly-gamma-glutamate synthetase (*FPGS*) activity is found in any cell undergoing sustained proliferative phases, but this enzyme also displays a tissue-specific pattern of expression in differentiated tissues. It is now reported that the steady state levels of *FPGS* mRNA in normal and neoplastic cells reflect these patterns, supporting the concept that the control mechanisms underlying this distribution are transcriptional. To initiate an understanding of these interacting levels of control, we have determined the position and properties of the minimal *FPGS* promoter controlling transcription of the *FPGS* *gene* in human CEM leukemia cells, a line which expresses high levels of this enzyme and its mRNA. The TATA-less region immediately upstream of the...

... a remarkably efficient promoter when used to drive expression of a luciferase reporter in transient expression studies in CEM cells. The minimal region of the *FPGS* promoter required for maximal transcriptional activation in CEM cells included the 80 base pairs over which the multiple transcriptional start sites were located, and the...

... which functioned as a minimal promoter in CEM cells. An additional region of the minimal promoter, situated between the two translational start codons of the *FPGS* *gene*, was bound by protein(s) from HeLa cell nuclear extracts. We conclude that transcription of the *FPGS* *gene* in CEM cells involves transactivation events over a limited upstream *DNA* sequence and that the *FPGS* promoter used in proliferating human leukemic cells has strong similarity to other TATA-less promoters that utilize tandem, closely spaced Sp1 sites to initiate transcription.
Tags: *Animal*;
Descriptors: *Gene* Expression Regulation, Enzymologic; *Peptide Synthases--biosynthesis--BI; *Peptide Synthases--genetics--GE; *Promoter Regions (Genetics); *Transcription, Genetic; Base Sequence; Codon; *DNA* Probes; *Gene* Expression Regulation, Neoplastic; Genes, Reporter; Hela Cells; Leukemia; Mice; Molecular Sequence Data; Polymerase Chain Reaction; Recombinant Fusion Proteins--biosynthesis--BI; Regulatory Sequences, Nucleic Acid; Sequence...
Chemical Name: Codon; *DNA* Probes; Recombinant Fusion Proteins; Peptide Synthases; folylpolyglutamate synthetase

7/3,K/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09396316 97190284 PMID: 9038166
Additional organizational features of the murine folylpolyglutamate synthetase *gene*. Two remotely situated exons encoding an alternate 5' end and proximal open reading frame under the control of a second promoter.
Roy K; Mitsugi K; Sirotnak FM
Program of Molecular Pharmacology and Therapeutics, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.
Journal of biological chemistry (UNITED STATES) Feb 28 1997, 272 (9) p5587-93, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: CA08748, CA, NCI; CA56417, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Additional organizational features of the murine folylpolyglutamate synthetase *gene*. Two remotely situated exons encoding an alternate 5' end and proximal open reading frame under the control of a second promoter.
Nucleotide sequence analysis of independently isolated clones from a mouse liver *cDNA* library identified two additional splice variants of folylpolyglutamate synthetase (*FPGS*) mRNA with novel sequence at the 5' end. These variants incorporate two new alternatives (exons A1a and A1b) of exon 1 in the murine *FPGS* *gene* which are also spliced to exon 2. Exon A1a encodes most of the 5'-untranslated region. Exon A1b encodes a downstream segment of the 5'-untranslated region, two ATG start codons, and a unique mitochondrial leader peptide as well as 15 additional amino acids of cytosolic *FPGS* not encoded by all previously identified (Roy, K., Mitsugi, K., and Sirotnak, F. M. (1996) J. Biol. Chem., 271, 23820-23827) splice variants. It was...

... content of putative cis-acting elements. Primer extension analysis identified a number of potential transcription start sites within the more 3' end of this region. *FPGS* RNA transcripts incorporating exons A1a and A1b were detected in both normal mouse tissues, particularly, liver and kidney, and also to a varying extent in tumors; *FPGS* RNA transcripts incorporating exons B1a, B1b, and B1c were detected mainly in tumors. Thus, transcription of the *FPGS* *gene* in this tissue-specific manner appears to reflect the different usage of alternates to exon 1 under the control of different promoters. An unusual splice variant identified infrequently in a mouse liver *cDNA* library was 2.67 kilobases in size and incorporated exons A1a and A1b and a segment of the downstream promoter region along with exons B1c...
Tags: *Animal*;
; Alternative Splicing; Amino Acid Sequence; Base Sequence; Blotting, Northern; *DNA*, Complementary--chemistry--CH; Mice; Molecular Sequence Data; Restriction Mapping; Transcription, Genetic
Chemical Name: *DNA*, Complementary; Peptide Synthases; folylpolyglutamate synthetase

7/3,K/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09396295 97207242 PMID: 9054377
Posttranscriptionally mediated decreases in folylpolyglutamate synthetase *gene* expression in some folate analogue-resistant variants of the L1210 cell. Evidence for an altered cognate mRNA in the variants affecting the rate of de novo synthesis of the enzyme.
Roy K; Egan MG; Sirlin S; Sirotnak FM
Program in Molecular Pharmacology and Therapeutics, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.
Journal of biological chemistry (UNITED STATES) Mar 14 1997, 272 (11) p6903-8, ISSN 0021-9258 Journal Code: HIV

Contract/Grant No.: CA08748, CA, NCI; CA56517, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Posttranscriptionally mediated decreases in folylpolyglutamate synthetase *gene* expression in some folate analogue-resistant variants of the L1210 cell. Evidence for an altered cognate mRNA in the variants affecting the rate of de...

...selected, seven (L1210/EDX-4 to -7 and L1210/EDX-12 to -14) were found to exhibit 2-23-fold lower levels of folylpolyglutamate synthetase (*FPGS*) activity compared with parental L1210 cells. Lower levels of *FPGS* activity in cell-free extract from these variants using EDX as substrate were characterized by the same relative decrease in value for Vmax with no change in apparent Km. The results of an analysis of *FPGS* activity in mixtures of variant and parental cell extract suggested that no endogenous inhibitors in the variant cells or stimulatory factors in parental cells accounted for the differences observed. Also, *FPGS* from variant and parental cells showed no difference in thermostability. Decreases in a 60-61-kDa protein as shown by immunoblotting with anti-*FPGS* peptide antibody were found to occur commensurately with the decrease in *FPGS* activity in cell extract from the variants compared with parental cells. However, no evidence was obtained for a difference in turnover of *FPGS* protein during measurement of the decay of *FPGS* activity in cycloheximide-treated variant and parental cells. In addition, Northern blotting of poly(A)+ RNA did not reveal any difference in the size or level of *FPGS* mRNA among these various cell types. Studies of in vitro translation of hybridization-selected *FPGS* mRNA from L1210 cells showed that both mitochondrial and cytosolic forms of *FPGS* were generated during the reaction. Moreover, *FPGS* mRNA from the variant cells was significantly less effective in mediating formation of the *FPGS* peptide product in a manner correlating with *FPGS* activity and protein found in the cytosol of the various cell types. These results suggest that *FPGS* *gene* expression in these variants is posttranscriptionally altered at the level of the cognate mRNA itself and that this alteration constitutively down-regulates the steady-state level of *FPGS* in these variants.

Tags: *Animal*;
Descriptors: Aminopterin--analogs and derivatives--AA; *Drug Resistance --genetics--GE; *Folic Acid Antagonists--administration and dosage--AD; * *Gene* Expression Regulation, Enzymologic; *Peptide Synthases--genetics--GE

7/3,K/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09190964 96394505 PMID: 8798611
Organization and alternate splicing of the murine folylpolyglutamate synthetase *gene* . Different splice variants in L1210 cells encode mitochondrial or cytosolic forms of the enzyme.
Roy K; Mitsugi K; Sirotnak FM
Program in Molecular Pharmacology and Therapeutics, Memorial Sloan-Kettering Cancer Center, Cornell University, New York, New York 10021, USA.
Journal of biological chemistry (UNITED STATES) Sep 27 1996, 271 (39) p23820-7, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: CA08748, CA, NCI; CA56517, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Organization and alternate splicing of the murine folylpolyglutamate synthetase *gene* . Different splice variants in L1210 cells encode mitochondrial or cytosolic forms of the enzyme.

The organization of the murine folylpolyglutamate synthetase (*FPGS*) *gene* has been determined by sequence analysis that also revealed an interesting complexity in the case of exon 1. The entire nucleotide

sequence of the L1210 *FPGS* *cDNA*, the 3'- and 5'-untranslated regions, the mitochondrial leader sequence, and the coding region were found to be distributed on 15 exons with an overall length of 10.358 kilobases. Two splice variants of exon 1 were identified by screening of an L1210 cell *cDNA* library. Variant I (exons 1a + 1b plus 2-15) incorporates all of the sequence homologous to the recently reported (Taylor, S. M., Freemantle, S. J...

... Res. 55, 6030-6034) human exon 1, including two ATG start codons at positions +1 and +126, and encodes both mitochondrial and cytosolic form of *FPGS* . The most prevalent variant, Variant II (exons 1b plus 2 to 15), incorporates only a portion (92 nucleotides at the 3' end) of this sequence, incorporates only one ATG start codon at position +126, and encodes only cytosolic *FPGS*. The existence of this variant is consistent with the identification of an appropriately situated internal donor/acceptor site in what was believed to be exon 1. A third related variant (Variant III) with a novel 5' termini was originally identified by screening of a mouse liver *cDNA* library. This variant, which occurs at moderately low frequency in the L1210 cell *cDNA* library, incorporates an alternate to exon 1a (exon 1c) spliced to exon 1b plus exons 2-15 and encodes a different mitochondrial leader peptide than...
...of these variants suggests another possible mechanism, i.e. at the level of precursor mRNA splicing, for regulating synthesis of mitochondrial versus cytosolic forms of *FPGS* in the cell. Exon 1c is positioned in the *gene* upstream of exon 1a separated by an intron of 56 nucleotides within a region of *DNA* sequence that like the homologous human sequence is distinctly promoter-like. However, the sequence of this region differs from the human sequence in terms of...

Tags: *Animal*;
; Alternative Splicing; Amino Acid Sequence; Base Sequence; Cytosol --enzymology--EN; *DNA*, Complementary--genetics--GE; Exons; Leukemia L1210 --enzymology--EN; Mice; Mitochondria--enzymology--EN; Molecular Sequence Data; Regulatory Sequences, Nucleic Acid; Sequence Alignment; Sequence Homology, Amino Acid

Chemical Name: *DNA*, Complementary; Peptide Synthases; folylpolyglutamate synthetase

7/3,K/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09184749 96278709 PMID: 8662720

Purification and properties of human cytosolic folylpoly-gamma-glutamate synthetase and organization, localization, and differential splicing of its *gene*.

Chen L; Qi H; Korenberg J; Garrow TA; Choi YJ; Shane B
Department of Nutritional Sciences, University of California, Berkeley, California 94720, USA.

Journal of biological chemistry (UNITED STATES) May 31 1996, 271 (22) p13077-87, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: CA-41991, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Purification and properties of human cytosolic folylpoly-gamma-glutamate synthetase and organization, localization, and differential splicing of its *gene*.

Human cytosolic folylpolyglutamate synthetase (*FPGS*) was expressed in Escherichia coli and purified to homogeneity. Tetrahydrofolate and dihydrofolate were the most effective substrates, while 5-substituted folates were poor substrates. Most pteroyldiglutamates were better substrates than monoglutamates. The human *FPGS* *gene* spans 12 kilobases and contains 15 exons and 14 introns. A single *FPGS* *gene* was located to chromosome region 9q34.1. Four exon 1 variants were identified, each of which was spliced to exon 2. The exon 1 variant corresponding to the

isolated *cDNA* contains two ATG codons and multiple transcription start sites in this region generates mitochondrial and cytosolic *FPGS* (Freemantle, S. J., Taylor, S. M., Krystal, G., and Moran, R. G. (1995) J. Biol. Chem. 270, 9579-9584). Exons 1B and 1C, generated by...

... to exon 1 and may encode an additional mitochondrial isoform, are preceded by a number of potential promoter sites. Chinese hamster ovary cell transfectants expressing *FPGS* activity in the mitochondria contained normal mitochondrial and low cytosolic folylpolyglutamate pools. Mitochondrial *FPGS* activity is required for mitochondrial folate accumulation, while cytosolic *FPGS* activity is needed for establishment of normal cytosolic folate pools. The reconstructed *FPGS* *gene* restored normal cytosolic and mitochondrial folate metabolism in hamster cells.

Tags: *Animal*;

; Amino Acid Sequence; Base Sequence; CHO Cells; Chromatography, Ion Exchange; Chromosome Mapping; Chromosomes, Human, Pair 9; Cloning, Molecular; *DNA*, Complementary; Electrophoresis, Polyacrylamide Gel; Escherichia coli--genetics--GE; Exons; Folic Acid--metabolism--ME; Hamsters ; Introns; Isoenzymes--genetics--GE; Isoenzymes--metabolism--ME; Molecular Sequence Data; Peptide...

Chemical Name: *DNA*, Complementary; Isoenzymes; Folic Acid; Peptide Synthases; folylpolyglutamate synthetase

7/3,K/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08866943 96180977 PMID: 8605241
Molecular cloning of murine folylpoly-gamma-glutamate synthetase.
Spinella MJ; Brigle KE; GoldmanD
Department of Medicine, Virgigina Commonwealth University, Medical College of Virginia, Richmond, VA 23298, USA.
Biochimica et biophysica acta (NETHERLANDS) Feb 7 1996, 1305 (1-2) p11-4, ISSN 0006-3002 Journal Code: A0W
Contract/Grant No.: CA-09349, CA, NCI; CA-39807, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Folylpoly-gamma-glutamate synthetase (*FPGS*) is essential for mammallian cell survival and is a major determinant of cytotoxicity and selectivity for folate antimetabolites. Here we describe the cloning of a *cDNA* encoding murine *FPGS* isolated from L1210 leukemia cells. The amino acid sequence of murine *FPGS* is 82% identical to human *FPGS*+[1] with identical discrete regions of up to 41 residues. Murine *FPGS* contains two AUG initiation codons, shown to be responsible for mitochondrial and cytosolic forms of the enzyme in human cells [2] Previous studies indicated species, tissue, and tumor specific differences in mammalian *FPGS*. The availability of murine *FPGS* expands the knowledge and understanding of the spectrum of these variations.

Tags: *Animal*;

; Amino Acid Sequence; Base Sequence; Cloning, Molecular; *DNA* , Complementary; Escherichia coli--genetics--GE; Lactobacillus--enzymology --EN; Lactobacillus--genetics--GE; Leukemia L1210--enzymology--EN; Leukemia L1210--genetics--GE; Mice; Molecular Sequence Data; Sequence Homology...

Chemical Name: *DNA*, Complementary; Peptide Synthases; folylpolyglutamate synthetase

7/3,K/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08801110 96070787 PMID: 7592937
Different antifolate-resistant L1210 cell variants with either increased or decreased folylpolyglutamate synthetase *gene* expression at the level

of mRNA transcription.
Roy K; Mitsugi K; Sirlin S; Shane B; Sirotnak FM
Program in Molecular Pharmacology and Therapeutics, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.
Journal of biological chemistry (UNITED STATES) Nov 10 1995, 270 (45) p26918-22, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: CA08748, CA, NCI; CA56517, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Different antifolate-resistant L1210 cell variants with either increased or decreased folylpolyglutamate synthetase *gene* expression at the level of mRNA transcription.
... R84) with further reduction in one-carbon, reduced folate transport and in two cases (L1210/R83 and R84) with 3-8-fold increased folylpolyglutamate synthetase (*FPGS*) activity and folate compound polyglutamate formation in situ. Metoprine resistance was further increased, and the requirement for exogenous folate during growth was decreased as well in these variants. The increase in *FPGS* activity observed in L1210/R83 and R84 was characterized by 3- and 8-fold increases in value for Vmax with no change in Km and...

... 61-kDa protein as shown by immunoblotting. Northern blotting revealed the same increases in these two variants in the level of a 2.3-kilobase *FPGS* mRNA when compared with control, while Southern blotting of genomic *DNA* did not reveal any increase in *FPGS* *gene* -copy number or restriction polymorphisms. Also, no difference in stability of *FPGS* mRNA was found between parental and variant cells. In contrast, nuclear run-on assays revealed differences among these cell types in the rate of *FPGS* mRNA transcription that correlated with increased *FPGS* activity, protein, and mRNA level in the variants. Similar studies with a transport-defective, methotrexate-resistant L1210 cell variant (L1210/R25) documented a 2-3-fold decrease in *FPGS* activity, protein, and mRNA levels that was accounted for by a decrease in *FPGS* mRNA transcription. These results provide the first examples of constitutively altered transcriptional regulation of *FPGS* activity associated with acquired resistance to antifolates.
Tags: *Animal*;
; Amino Acid Sequence; Drug Resistance; Folic Acid Antagonists --pharmacology--PD; *Gene* Amplification; *Gene* Expression; Leukemia L1210 --drug therapy--DT; Mice; Molecular Sequence Data; Peptide Synthases --metabolism--ME; Pyrimethamine--analogs and derivatives--AA; Pyrimethamine--pharmacology--PD; RNA, Messenger--metabolism...

7/3,K/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08767329 95238480 PMID: 7721888
Upstream organization of and multiple transcripts from the human folylpoly-gamma-glutamate synthetase *gene*.
Freemantle SJ; Taylor SM; Krystal G; Moran RG
Department of Pharmacology and Toxicology, Medical College of Virginia, Richmond 23298-0230, USA.
Journal of biological chemistry (UNITED STATES) Apr 21 1995, 270 (16) p9579-84, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: CA 27605, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Upstream organization of and multiple transcripts from the human folylpoly-gamma-glutamate synthetase *gene*.
Folylpoly-gamma-glutamate synthetase (*FPGS*) is essential for the survival of proliferating mammalian cells and central to the action of all

"classical" folate antimetabolites. We report the isolation of cDNAs corresponding to the 5' ends of *FPGS* mRNA from both human and hamster cells which include a start codon upstream of and in-frame with the AUG in the previously reported *FPGS* open reading frame. The predicted hamster and human amino-terminal extension peptides have features consistent with a mitochondrial targeting sequence. Ribonuclease protection and 5'-rapid amplification of *cDNA* ends assays indicated multiple transcriptional start sites consistent with the sequence of the promoter region of this *gene* , which was highly GC-rich and did not contain TATA or CCAAT elements. These start sites would generate two classes of transcripts, one including the upstream AUG and one in which only the downstream AUG would be available for translation initiation. Transfection of the full length human *cDNA* into cells lacking *FPGS* restored their ability to grow in the absence of glycine, a product of mitochondrial folate metabolism, as well as of thymidine and purines. Therefore, we propose that the mitochondrial and cytosolic forms of *FPGS* are derived from the same *gene* , arising from the use of the two different translation initiation codons, and that the translation products differ by the presence of a 42-residue amino...
Tags: *Animal*;

7/3,K/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08450263 95170143 PMID: 7865908
Quantitative analysis of folylpolyglutamate synthetase *gene* expression in tumor tissues by the polymerase chain reaction: marked variation of expression among leukemia patients.
Lenz HJ; Danenberg K; Schnieders B; Goeker E; Peters GJ; Garrow T; Shane B; Bertino JR; Danenberg PV
Kenneth T. Norris Jr. Cancer Hospital and Research Institute, University of Southern California, Los Angeles 90033.
Oncology research (UNITED STATES) 1994, 6 (7) p329-35, ISSN 0965-0407 Journal Code: BBN
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Quantitative analysis of folylpolyglutamate synthetase *gene* expression in tumor tissues by the polymerase chain reaction: marked variation of expression among leukemia patients.
Evidence from previous in vitro studies indicates that the enzyme folylpolyglutamate synthetase (*FPGS*) may be an important determinant of the antitumor activity of antifolate drugs that are substrates for this enzyme. To facilitate investigations regarding the association between *FPGS* content of tumor tissues and the sensitivity of tumors to antifolates, we developed a polymerase chain reaction (PCR)-based *gene* expression quantitation assay for measuring relative amounts of *FPGS* mRNA in tumor tissue specimens. From the known sequence of the human *gene*, *FPGS* -specific PCR primers were chosen that flanked a 263-base segment of the *FPGS* *gene*. The PCR carried out with these primers was linear over at least a three orders of magnitude range of starting *cDNA* concentration. The amount of *cDNA* required per assay corresponded to the quantity of RNA contained in nanogram to microgram amounts of tissue, depending on the level of *gene* expression. In CHO AUXB1 (*FPGS*) cell lines transfected with human *DNA* and expressing different levels of human *FPGS*, *FPGS* *gene* expression measured by this assay was linear with the *FPGS* enzyme activity in the cells. In human head and neck cell lines, which contained naturally varying levels of *FPGS* enzyme activity, *FPGS* *gene* expressions were also linearly proportional to *FPGS* enzyme content as measured both by activity in cell-free extracts and by intracellular methotrexate polyglutamate formation. Among leukemic cells from 11 acute lymphocytic leukemia and acute myelogenous leukemia patients, *FPGS* expression varied by over 500-fold.(ABSTRACT TRUNCATED AT 250 WORDS)
Tags: *Animal*;

Descriptors: *Gene* Expression; *Leukemia--enzymology--EN; *Peptide Synthases--biosynthesis--BI; Actins--biosynthesis--BI; Base Sequence; Blast Crisis--genetics--GE; CHO Cells; *DNA* Primers; Hamsters; Leukemia --pathology--PA; Leukemia, Lymphocytic, Acute--enzymology--EN; Leukemia, Lymphocytic, Acute--pathology--PA; Leukemia, Myelocytic, Acute--enzymology --EN; Leukemia, Myelocytic, Acute--pathology--PA...
Chemical Name: Actins; *DNA* Primers; Peptide Synthases; folylpolyglutamate synthetase
?ds

Set	Items	Description
S1	609	(FPGS OR (FOLYLPOLYGLUTAMYL (W) SYNTHETASE))
S2	13	S1 AND REVIEW
S3	11	RD (unique items)
S4	195	S1 AND (GENE OR CDNA OR DNA)
S5	1	S4 AND REVIEW
S6	61	S4 AND (MAMMAL OR ANIMAL)
S7	35	RD (unique items)

?t s7/3,k/21-35

7/3,K/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08239116 94375001 PMID: 8088777
Genetic linkage analysis of the Ak1, Col5a1, Epb7.2, *Fpgs*, Grp78, Pbx3, and Notch1 genes in the region of mouse chromosome 2 homologous to human chromosome 9q.
Pilz A; Prohaska R; Peters J; Abbott C
Department of Genetics and Biometry, University College London, United Kingdom.
Genomics (UNITED STATES) May 1 1994, 21 (1) p104-9, ISSN 0888-7543 Journal Code: GEN
Contract/Grant No.: 2S07RR056545, RR, NCRR
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Genetic linkage analysis of the Ak1, Col5a1, Epb7.2, *Fpgs*, Grp78, Pbx3, and Notch1 genes in the region of mouse chromosome 2 homologous to human chromosome 9q.
The genes for adenylate kinase-1 (AK1), folyl polyglutamate synthetase (*FPGS*), the collagen pro alpha 1(V) chain (COL5A1), erythrocyte protein band 7.2b (EPB72), and a proto-oncogene homeobox (PBX3) all map to the distal...
... have used two interspecific backcrosses to map the mouse homologues of each of these genes to mouse chromosome 2 (MMU2). The Ak1, Col5a1, Epb7.2, *Fpgs* , and Pbx3 genes were mapped with respect to the genes for Grp78, Rxra, Notch1 (the mouse homologue of TAN1), Spna2, Abl, and Hc (the mouse ...

...Two of the reference loci for MMU2, D2Mit1 and Acra, were also mapped in the same cross to facilitate comparisons with existing maps. The consensus *gene* order deduced by combining data from both crosses is D2Mit1-(Dbh,Notch1)-(Col5a1,Rxra)-Spna2-Ab 1-(Ak1,*Fpgs*)- (Grp78,Pbx3)-(Epb7.2,Hc,Gsn)-Acra. These loci therefore form part of the conserved synteny between HSA9q and MMU2.
Tags: *Animal*;
Gene Symbol: ist/GeneSymbol AK1FPGS; ist/GeneSymbol Ak1; ist/GeneSymbol COL5A1; ist/GeneSymbol Col5a1; ist/GeneSymbol EPB72; ist/GeneSymbol Epb7.2; ist/GeneSymbol *Fpgs*; ist/GeneSymbol Grp78; ist/GeneSymbol PBX3; ist/GeneSymbol Pbx3

7/3,K/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08046068 94012745 PMID: 8408018

Regulation of folate and one-carbon metabolism in mammalian cells. I. Folate metabolism in Chinese hamster ovary cells expressing Escherichia coli or human folylpoly-gamma-glutamate synthetase activity.

Osborne CB; Lowe KE; Shane B

Department of Nutritional Sciences, University of California, Berkeley 94720.

Journal of biological chemistry (UNITED STATES) Oct 15 1993, 268 (29) p21657-64, ISSN 0021-9258 Journal Code: HIV

Contract/Grant No.: CA-41991, CA, NCI; GM073079, GM, NIGMS

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Chinese hamster ovary (CHO) cell transfectants expressing various levels of human and Escherichia coli folylpoly-gamma-glutamate synthetase (*FPGS*) activity and possessing different folylpolyglutamate chain length distributions have been developed as models for folate and antifolate metabolism. The synthesis of pteroyltriglutamate was sufficient for normal cellular retention of folate and also overcame the phenotypic requirement for purines and thymidine of AUXB1, a CHO cell mutant lacking *FPGS* activity and lacking folylpolyglutamates. Only low levels of *FPGS* are required to enable cellular metabolism of folates to forms that are retained by mammalian cells. The higher levels found in mammalian cells are required for the synthesis of the long chain polyglutamate derivatives characteristic of mammalian cells. At low medium folate concentrations, folate accumulation by transfectants expressing human *FPGS* was not responsive to *FPGS* levels as the limiting step in metabolism was beyond the triglutamate, the chain length required for retention. The rate-limiting step in folate metabolism in cells expressing the E. coli enzyme was the conversion of diglutamate to triglutamate, and, at low *FPGS* levels, the E. coli enzyme was about 50-fold less effective than the human *FPGS* in enabling cellular folate accumulation. These data suggest that cellular accumulation of any folate analog whose mono- or diglutamate derivative is a poor substrate for *FPGS* would be very responsive to the level of *FPGS* activity.

Tags: *Animal*;

; Base Sequence; CHO Cells; Cells, Cultured; Cloning, Molecular; *DNA*, Bacterial; Hamsters; Molecular Sequence Data; Peptide Synthases--genetics --GE; Transfection

Gene Symbol: ist/GeneSymbol *FPGS*; ist/GeneSymbol folC

Chemical Name: *DNA*, Bacterial; Folic Acid; Carbon; Peptide Synthases; folylpolyglutamate synthetase

7/3,K/23 (Item 23 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

07809966 93028422 PMID: 1409616

Expression cloning of a human *cDNA* encoding folylpoly(gamma-glutamate) synthetase and determination of its primary structure.

Garrow TA; Admon A; Shane B

Department of Nutritional Sciences, University of California, Berkeley 94720.

Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Oct 1 1992, 89 (19) p9151-5, ISSN 0027-8424 Journal Code: PV3

Contract/Grant No.: CA41991, CA, NCI

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Expression cloning of a human *cDNA* encoding folylpoly(gamma-glutamate) synthetase and determination of its primary structure.

A human *cDNA* for folypoly(gamma-glutamate) synthetase [*FPGS* ; tetrahydrofolate:L-glutamate gamma-ligase (ADP forming), EC 6.3.2.17] has

been cloned by functional complementation of an Escherichia coli folC mutant. The *cDNA* encodes a 545-residue protein of M(r) 60,128. The deduced sequence has regions that are highly homologous to peptide sequences obtained from purified pig liver *FPGS* and shows limited homology to the E. coli and Lactobacillus casei FPGSs. Expression of the *cDNA* in E. coli results in elevated expression of an enzyme with characteristics of mammalian *FPGS*. Expression of the *cDNA* in AUXB1, a mammalian cell lacking *FPGS* activity, overcomes the cell's requirement for thymidine and purines but does not overcome the cell's glycine auxotrophy, consistent with expression of the protein...
Tags: *Animal*;
Descriptors: *DNA*--genetics--GE; *Peptide Synthases--genetics--GE; Amino Acid Sequence; Base Sequence; Cloning, Molecular; Escherichia coli --enzymology--EN; Escherichia coli--genetics--GE; *Gene* Expression; *Gene* Library; Kinetics; Lactobacillus casei--enzymology--EN; Lactobacillus casei--genetics--GE; Liver--enzymology--EN; Molecular Sequence Data; Mutagenesis, Site-Directed; Peptide Synthases--isolation and purification--IP...
Chemical Name: Recombinant Proteins; *DNA*; Peptide Synthases; folylpolyglutamate synthetase

7/3,K/24 (Item 24 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06954746 90228970 PMID: 1970331
Assignment of the structural *gene* for argininosuccinate synthetase to proximal mouse chromosome 2.
Jackson MJ; Surh LC; O'Brien WE; Beaudet AL
Howard Hughes Medical Institute, Baylor College of Medicine, Houston, Texas 77030.
Genomics (UNITED STATES) Mar 1990, 6 (3) p545-7, ISSN 0888-7543 Journal Code: GEN
Contract/Grant No.: GM 27593, GM, NIGMS; RR05425-26, RR, NCRR
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Assignment of the structural *gene* for argininosuccinate synthetase to proximal mouse chromosome 2.
... synthetase locus (Ass-1), we have searched for restriction fragment length polymorphisms in the mouse genome using cloned sequences from the mouse arginosuccinate synthetase structural *gene* . Five restriction fragment length polymorphisms were found among the recombinant inbred progenitor strains AKR/J, BALB/cByJ, C3H/HeJ, C57BL/6J, C57L/J, DBA/2J...
... and a 95% confidence interval of 0.003 to 0.054. These data place Ass-1 in a syntenic group with the genes Hc, Abl, *Fpgs*, and Ak-1 whose linkage has been conserved between human chromosome 9q and mouse chromosome 2.
Tags: *Animal*;

7/3,K/25 (Item 25 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06000027 87070133 PMID: 3466358
Characterization of human folylpolyglutamate synthetase expressed in Chinese hamster ovary cells.
Sussman DJ; Milman G; Shane B
Somatic cell and molecular genetics (UNITED STATES) Nov 1986, 12 (6) p531-40, ISSN 0740-7750 Journal Code: UY2
Contract/Grant No.: CA01160, CA, NCI; CA41991, CA, NCI; GM32950, GM, NIGMS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Chinese hamster AUX B1 cells lack the enzyme folylpolyglutamate synthetase (*FPGS*) responsible for adding polyglutamates to folic acid. The human *gene* for *FPGS* was introduced into AUX B1 cells by cotransfection with human genomic *DNA* and either pSV2neo or pSV2gpt plasmid *DNA*. Cells were coselected for *FPGS* expression by growth in the absence of glycine, adenosine, and thymidine, and for drug resistance by growth in geneticin or mycophenolic acid. The presence of...

... in AUX B1 cells, while wild-type hamster cells had predominantly hexa- and heptaglutamates, and human HeLa cells had predominantly hepta- and octaglutamates. Transformants with *FPGS* activity that showed a human enzyme preference for dATP also had folate polyglutamate chain lengths characteristic of the human enzyme.

Tags: *Animal*;

7/3,K/26 (Item 26 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05894715 87125748 PMID: 3812977

In situ autoradiographic detection of folylpolyglutamate synthetase activity.

Sussman DJ; Milman G; Osborne C; Shane B

Analytical biochemistry (UNITED STATES) Nov 1 1986, 158 (2) p371-6, ISSN 0003-2697 Journal Code: 4NK

Contract/Grant No.: CA41991, CA, NCI; GM32950, GM, NIGMS

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The enzyme folylpolyglutamate synthetase (*FPGS*) catalyzes the conversion of folate (pteroylmonoglutamate) to the polyglutamate forms (pteroylpolyglutamates) that are required for folate retention by mammalian cells. A rapid in situ autoradiographic assay for *FPGS* was developed which is based on the folate cofactor requirement of thymidylate synthase. Chinese hamster AUX B1 mutant cells lack *FPGS* activity and are unable to accumulate folate. As a result, the conversion of [6-3H]deoxyuridine to thymidine via the thymidylate synthase reaction is impaired in AUX B1 cells and no detectable label is incorporated into *DNA*. In contrast, *FPGS* in wild-type Chinese hamster CHO cells causes folate retention and enables the incorporation of [6-3H]deoxyuridine into *DNA* . Incorporation may be detected by autoradiography of monolayer cultures or of colonies replica plated onto polyester discs. Introduction of Escherichia coli *FPGS* into AUX B1 cells restores the activity of the thymidylate synthase pathway and demonstrates that the E. coli *FPGS* enzyme can provide pteroylpolyglutamates which function in mammalian cells.

Tags: *Animal*;

; Autoradiography; Cell Line; *DNA*--biosynthesis--BI; Deoxyuridine --metabolism--ME; Folic Acid--metabolism--ME; Hamsters; Thymidylate Synthase--metabolism--ME

Chemical Name: Folic Acid; *DNA*; Deoxyuridine; Thymidylate Synthase; Peptide Synthases; folylpolyglutamate synthetase

7/3,K/27 (Item 27 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05868545 85296071 PMID: 3839900

Induced reversion of a Chinese hamster ovary triple auxotroph. Validation of the system with several mutagens.

Taylor RT; Wu R; Hanna ML

Mutation research (NETHERLANDS) Sep 1985, 151 (2) p293-308, ISSN 0027-5107 Journal Code: NNA

Contract/Grant No.: R01 ES02848, ES, NIEHS

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

A Chinese hamster ovary triple auxotroph (CHO AUXB1) requires glycine, adenosine, and thymidine (GAT) for growth and survival due to a defect in the structural *gene* for folylpolyglutamate synthetase (*FPGS*). This auxotroph and others like it contain less than 3% of the parental amounts of *FPGS* activity. In order to develop a reverse mutation assay with CHO AUXB1, we determined the optimal conditions for measuring reversion and characterized some of the...

...42 that have been analyzed are characterized by an increased 72-h growth incorporation of labeled folate and their extracts contain 5-94% as much *FPGS* as the original, parental CHO-S line. Spontaneous and induced reversion to the GAT+ phenotype primarily reflects mutations involving the *FPGS* *gene* locus. But the re-acquisition by most of the revertants of much less than normal amounts of *FPGS* activity suggests that they arise from compensatory second-site mutations within this *gene*. Comparison of the mutagenicity patterns of the foregoing compounds as a function of the applied concentration and the relative percent survival reveals some interesting similarities, as well as differences, between the CHO AUXB1/ *FPGS* and CHO-S/HGPRT loci. In particular, the *FPGS* locus is rather insensitive to EMS (or other simple alkylating agents). However, it seems to be quite susceptible to reversion by other chemicals that are known to react selectively with guanine bases in *DNA* . CHO AUXBI is a useful supplemental mammalian assay system for assessing quantitatively the generally weak mutagenic activities of metal compounds.
Tags: *Animal*;

7/3,K/28 (Item 28 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04085833 81065955 PMID: 6934068
Chromosomal assignment of the *gene* for folylpolyglutamate synthetase to human chromosome 9.
Jones C; Kao FT; Taylor RT
Cytogenetics and cell genetics (SWITZERLAND) 1980, 28 (3) p181-94, ISSN 0301-0171 Journal Code: DXK
Contract/Grant No.: CA-18734, CA, NCI; CA-20810, CA, NCI; HD-02080, HD, NICHD
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Chromosomal assignment of the *gene* for folylpolyglutamate synthetase to human chromosome 9.
... and exhibiting multiple growth requirements for glycine, adenine, and thymidine, has been shown to be deficient in one of the folate-dependent enzymes, folylpolyglutamate synthetase (*FPGS*). This mutant was fused with normal human lymphocytes and human lymphoblasts and 41 GAT+ primary hybrid clones were isolated in medium lacking glycine, adenine, and...

...marker and AK1, an isozyme marker for human chromosome 9. Enzyme studies of the parental and hybrid cells not only showed restored enzyme activities of *FPGS* in the hybrids, but also demonstrated that several enzyme characteristics of *FPGS* in the hybrids are consistent with those of the human enzyme. Thus, it is concluded that the human *gene* coding for the enzyme *FPGS* which complements the auxotrophic mutant GAT- in the CHO-K1 cells can be assigned to human chromosome 9. This assignment provides an additional selective marker...
Tags: *Animal*;

7/3,K/29 (Item 29 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04067056 83171874 PMID: 6687641
Complementation mapping in microcell hybrids: localization of *Fpgs* and Ak-1 on Mus musculus chromosome 2.
Fournier RE; Moran RG
Somatic cell genetics (UNITED STATES) Jan 1983, 9 (1) p69-84, ISSN 0098-0366 Journal Code: VAJ
Contract/Grant No.: CA27605, CA, NCI; GM26449, GM, NIGMS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Complementation mapping in microcell hybrids: localization of *Fpgs* and Ak-1 on Mus musculus chromosome 2.
The *gene* encoding *folylpolyglutamyl* *synthetase* (*FPGS*) was assigned to mouse chromosome 2 by complementation mapping. Chinese hamster ovary cells (AuxBl) deficient in *FPGS*, and consequently auxotrophic for glycine, adenosine, and thymidine (gat-), were employed as recipients in microcell-mediated chromosome transfer experiments. Mouse chromosomes derived from diploid embryo...

... gat+ microcell hybrids were selected in medium lacking adenosine and thymidine. Mouse chromosome 2 was the only donor chromosome whose presence correlated with expression of *FPGS* activity. Furthermore, every gat+ hybrid clone expressed murine AK-1, a marker previously assigned to chromosome 2. Eight of 20 clones analyzed retained deletion chromosomes derived from mouse chromosome 2. These clones were used to localize murine *Fpgs* and Ak-1 to a region of this chromosome, namely 2 (cen leads to Cl).
Tags: *Animal*;

7/3,K/30 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12339326 BIOSIS NO.: 200000092828
Tissue-specific expression of functional isoforms of mouse folylpoly-gamma-glutamate synthetase: A basis for targeting folate antimetabolites.
AUTHOR: Turner Fiona B; Andreassi John L II; Ferguson Jennifer; Titus Steven; Tse Archie; Taylor Shirley M; Moran Richard G(a)
AUTHOR ADDRESS: (a)Massey Cancer Center, Medical College of Virginia, Virginia Commonwealth University, 401 College Street, Richmond, VA, 23298-0230**USA
JOURNAL: Cancer Research 59 (24):p6074-6079 Dec. 15, 1999
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Folates and folate antimetabolites are metabolically trapped in mammalian cells as polyglutamates, a process catalyzed by folylpoly-gamma-glutamate synthetase (*FPGS*). Using 5'-rapid amplification of *cDNA* ends, RNase protection assays, transfection of cDNAs into *FPGS*-deficient cells, and kinetic analysis of recombinant enzymes expressed in insect cells, it was determined that the species of active *FPGS* in mouse liver and kidney was different from that in mouse tumor cells, bone marrow, and intestine. The NH2-terminal peptide of hepatic enzyme contained...

...one of two alternative sets of initial coding exons in different tissues underlies this phenomenon, suggesting the design of antifolates specific for activation by individual *FPGS* isoforms and hence tissue-selective targeting of antifolate therapy for cancer, arthritis, or psoriasis.
DESCRIPTORS:
...ORGANISMS: *animal* model

7/3,K/31 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
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11193095 EMBASE No: 2001202350
Update on antifolate drugs targets
Costi M.P.; Ferrari S.
M.P. Costi, Dipartimento di Sci. Farmaceutiche, University of Modena/Reggio Emilia, via Campi 183, 41100 Modena Italy
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Current Drug Targets (CURR. DRUG TARGETS) (Netherlands) 2001, 2/2 (135-166)
CODEN: CDTUA ISSN: 1389-4501
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 106

...genetic level of molecular probes as antifolate drug to develop new enzymes previously unknown. This approach is defined as genetic approach to drug discovery, from *gene* to drugs. The present article describes the importance in drug design and discovery of some antifolate targets among the best known at the present status of research such as thymidylate synthase (TS), dhydrofolate reductases, (DHFR) serine hydroxymethyltransferase (SHMT), folyilpolyglutamyl synthetase (*FPGS*), gamma-glutamyl hydrolase (gamma-GH), glycinamide-ribonucleotide transformylase (GARTfase), amino-imidazole-carboxamide-ribonucleotide transformylase (AICARTfase) and Folate transporters. Discovery, known functions, structure/function studies and...
MEDICAL DESCRIPTORS:
...structure activity relation; competitive inhibition; antineoplastic activity; protozoal infection--drug therapy--dt; Pneumocystis carinii; Toxoplasma gondii; human; nonhuman; rat; clinical trial; controlled study; human cell; *animal* cell; article

7/3,K/32 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE
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10578711 EMBASE No: 2000043534
Two promoters regulate transcription of the mouse folylpolyglutamate synthetase geneThree tightly clustered Sp1 sites within the first intron markedly enhance activity of promoter B
Chen J.; Hayes P.; Roy K.; Sirotnak F.M.
F.M. Sirotnak, Program of Molecular Pharmacology, Memorial Sloan Kettering Cancer Ctr., Cornell University, New York, NY 10021 United States
AUTHOR EMAIL: sirotnaf@mskcc.org
Gene (GENE) (Netherlands) 2000, 242/1-2 (257-264)
CODEN: GENED ISSN: 0378-1119
PUBLISHER ITEM IDENTIFIER: S0378111999005077
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 23

The process of polyglutamylation mediated by folylpolyglutamate synthetase (*FPGS*) in mammalian cells has nutritional and pharmacological importance. In murine cells, *FPGS* expression is controlled by two promoters that, as we show here, vary substantially in their efficiency, at least in the context of a reporter *gene* assay. Characteristics of the most efficient promoter (promoter B) were examined in the present studies. Insertion in pGL3 of a 1635 bp segment of upstream...

...exon B1a resulted in a 15-20-fold increase in transcription in NIH3T3

and Hepl-6 cells compared with the promoterless vector. Deletion analysis of *DNA* sequence upstream of exon B1c showed that transcription was regulated by putative cis active elements only within two distally located upstream segments which when deleted...

...of and within exon B1c as well as downstream in exon B1a. This result is consistent with the frequent occurrence in murine cells of an *FPGS* variant (variant III) incorporating exon B1c [Roy et al., J. Biol. Chem. 271 (1996) 23 820; 272 (1997) 5587]. Site-directed mutagenesis and DNAse I ...

...we demonstrate that Sp1 can induce high levels of promoter B activity in pGL3 transfectants, but only when intron B1c is included within the reporter *gene* construct used. These results suggest that the unusually tight cluster of active Sp1 sites within intron B1c are essential and sufficient for maximal activity of...
MEDICAL DESCRIPTORS:
cell strain 3T3; site directed mutagenesis; polymerase chain reaction; *DNA* sequence; promoter region; reporter *gene*; genetic organization; transactivation; nonhuman; mouse; *animal* cell; article; priority journal

7/3,K/33 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2001 Elsevier Science B.V. All rts. reserv.

07460736 EMBASE No: 1998352007
Effects of antisense-based folylpoly-gamma-glutamate synthetase down-regulation on reduced folates and cellular proliferation in CCRF-CEM cells
Liu Y.; Raghunathan K.; Hill C.; He Y.; Bunni M.A.; Barredo J.; Priest D.G.
Dr. D.G. Priest, Department of Biochemistry, Medical University of South Carolina, 171 Ashley Avenue, Charleston, SC 29425 United States
Biochemical Pharmacology (BIOCHEM. PHARMACOL.) (United States) 1998, 55/12 (2031-2037)
CODEN: BCPCA ISSN: 0006-2952
PUBLISHER ITEM IDENTIFIER: S0006295298000896
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 29

The effect of down-regulation of folylpoly-gamma-glutamate synthetase (*FPGS*) activity on intracellular reduced folate accumulation and cellular proliferation was examined, using an inducible antisense expression system in the human T-lymphoblastic leukemia cell line CCRF-CEM. *FPGS* catalyzes the addition of gamma-glutamyl residues to natural folates and classical antifolates, which results in their enhanced cellular retention and increased cytotoxicity. As such...

...target. However, direct evidence to support this concept has been elusive. Hence, a study was undertaken using an antisense-based expression system to down-regulate *FPGS* activity. This inducible expression system was used to demonstrate that lower *FPGS* activity can lead to substantially lower intracellular folate content, which coincides with suppression of thymidylate synthesis and inhibition of cellular proliferation. Copyright (C) 1998 Elsevier...
MEDICAL DESCRIPTORS:
gene expression system; cell proliferation; reverse transcription polymerase chain reaction; rabbit; human; nonhuman; female; *animal* experiment; human cell; article; priority journal

7/3,K/34 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2001 Elsevier Science B.V. All rts. reserv.

05259549 EMBASE No: 1993027634
Determinants of antifolate cytotoxicity: Folylpolyglutamate synthetase activity during cellular proliferation and development
Barredo J.; Moran R.G.
Cancer Research Laboratories, Univ. of S. California Cancer Center, 1303 N. Mission Road,Los Angeles, CA 90033 United States
Molecular Pharmacology (MOL. PHARMACOL.) (United States) 1992, 42/4 (687-694)
CODEN: MOPMA ISSN: 0026-895X
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Previous studies have documented the metabolism of a broad range of folate antimetabolites to polyglutamate derivatives by the enzyme folylpoly-gamma- glutamate synthetase (*FPGS*). The activity of the more recently developed classes of antifolates directed against thymidylate synthase and de novo purine synthesis is sufficiently dependent on polyglutamation that these compounds should be specifically cytotoxic to any normal or malignant proliferating cell expressing this enzyme. We have studied the patterns of expression of *FPGS* in mammalian cells and tissues during rapid growth, growth arrest, differentiation, and embryonic development. During embryogenesis in the rat, *FPGS* levels in liver and brain were higher during the period of proliferative activity and then dropped to a level characteristic of the adult organs. However...

...were substantially higher than those in brain at any given time. This pattern was mimicked in mouse C3H 10T1/2 embryo fibroblast cells, in which *FPGS* activity decreased after cessation of growth but then remained at a lower steady state level during an extended period of postconfluent culture. Enzyme activity also dropped after the differentiation of human HL-60 promyelocytic leukemia cells. In a human homolog of these experimental systems, *FPGS* levels were below the limits of detection in circulating mature human hematopoietic cells of the granulocytic, lymphoblastic, and erythrocytic lineages. In striking contrast, substantial levels of *FPGS* were found in circulating lymphoblasts from eight patients with acute lymphoblastic leukemia. The levels of *FPGS* found in these transformed stem cells would help to explain the sensitivity of many acute lymphoblastic leukemias to folate antimetabolites. We concluded that expression of *FPGS* is regulated by at least two mechanisms, one of which is linked to proliferation and the other of which controls enzyme levels after differentiation and...
MEDICAL DESCRIPTORS:
animal cell; article; cell culture; cell differentiation; embryo development; enzyme localization; folate metabolism; *gene* expression; hematopoietic cell; human; human cell; leukemia cell; lymphoblast; nonhuman ; priority journal; purine synthesis; rat; tissue distribution

7/3,K/35 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2001 Elsevier Science B.V. All rts. reserv.

03735483 EMBASE No: 1988184919
Methotrexate analogues. 33.
N(delta)-acyl-N(alpha)-(4-amino-4-deoxypteroyl)-L-ornithine derivatives: Synthesis and in vitro antitumor activity
Rosowsky A.; Bader H.; Cucchi C.A.; Moran R.G.; Kohler W.; Freisheim J.H.
Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115 United States
Journal of Medicinal Chemistry (J. MED. CHEM.) (United States) 1988, 31/7 (1332-1337)
CODEN: JMCMA ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

N(delta)-Acyl derivatives of the potent folylpolyglutamate synthetase (*FPGS*) inhibitor N(alpha)-(4-amino-4-deoxypteroyl)-L-ornithine (APA-L-Orn) were synthesized from N(alpha)-(4-amino-4-deoxy-Nsup 1sup 0-formylpteroyl ...

...formyl group is well tolerated for DHFR binding. While N(2d)-acylation of APA-L-Orn did not significantly alter anti-DHFR activity, inhibition of *FPGS* was dramatically diminished, supporting the view that the basic NHinf 2 on the end of the APA-L-Orn side chain is essential for the activity of this compound against *FPGS*. N(delta)-Acylation of APA-L-Orn markedly enhanced toxicity to cultured tumor cells. However, N(delta)-acyl derivatives also containing an Nsup 1sup 0...

...assay is that they are efficiently taken up by the cell and are then cleaved to APA-L-Orn, which can simultaneously inhibit DHFR and *FPGS*, thereby acting as a 'self-potentiating antifolate'. According to this view, blockade of cellular *FPGS* activity should complement DHFR inhibition by diminishing the cell's ability to convert tetrahydrofolate monoglutamate cofactors to polyglutamates, which are the most efficiently used species for *DNA* precursor synthesis.
MEDICAL DESCRIPTORS:
carcinoma cell; cell culture; enzyme inhibition; leukemia cell; mouse; structure activity relation; human cell; *animal* cell; human; nonhuman
?ds

Set	Items	Description
S1	609	(FPGS OR (FOLYLPOLYGLUTAMYL (W) SYNTHETASE))
S2	13	S1 AND REVIEW
S3	11	RD (unique items)
S4	195	S1 AND (GENE OR CDNA OR DNA)
S5	1	S4 AND REVIEW
S6	61	S4 AND (MAMMAL OR ANIMAL)
S7	35	RD (unique items)

```
?s s1 and (cancer or (neoplatic (w) cell) or tumor or tumour)
             609  S1
         1991399  CANCER
              36  NEOPLATIC
         6074196  CELL
               2  NEOPLATIC(W)CELL
         1872678  TUMOR
          241807  TUMOUR
      S8     355  S1 AND (CANCER OR (NEOPLATIC (W) CELL) OR TUMOR OR
                  TUMOUR)
?s s8 and (antifolate or methotrexate or edatrexate or aminopterin or (thymidylate (w)
synthetase (w) inhibitor))
             355  S8
            3306  ANTIFOLATE
          124476  METHOTREXATE
             706  EDATREXATE
            3946  AMINOPTERIN
           12659  THYMIDYLATE
           87828  SYNTHETASE
          736394  INHIBITOR
              46  THYMIDYLATE(W)SYNTHETASE(W)INHIBITOR
      S9     233  S8 AND (ANTIFOLATE OR METHOTREXATE OR EDATREXATE OR
                  AMINOPTERIN OR (THYMIDYLATE (W) SYNTHETASE (W)
                  INHIBITOR))
?s s9 and (vector)
             233  S9
          183964  VECTOR
     S10       6  S9 AND (VECTOR)
?rd
...completed examining records
     S11       2  RD (unique items)
?t s11/3,k/all
```

11/3,K/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11381969 21282747 PMID: 11389096
Effects of overexpression of gamma-Glutamyl hydrolase on *methotrexate* metabolism and resistance.
Cole PD; Kamen BA; Gorlick R; Banerjee D; Smith AK; Magill E; Bertino JR
Department of Pediatrics, The Cancer Institute of New Jersey/Robert Wood Johnson University Hospital, 195 Little Albany Street, New Brunswick, NJ 08901, USA. colepd@umdnj.edu
Cancer research (United States) Jun 1 2001, 61 (11) p4599-604, ISSN 0008-5472 Journal Code: CNF
Contract/Grant No.: CA09512, CA, NCI; CA25933, CA, NCI; CA82425, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Effects of overexpression of gamma-Glutamyl hydrolase on *methotrexate* metabolism and resistance.
Intracellular metabolism of *methotrexate* (MTX) to MTX-polyglutamates (MTXPG) is one determinant of cytotoxicity. Steady-state accumulation of MTXPG seems to depend on the activity of two enzymes: folylpolyglutamate synthetase (*FPGS*), which adds glutamate residues, and gamma-glutamyl hydrolase (GGH), which removes them. Overexpression of GGH would be expected to decrease intracellular MTXPG, thereby increasing efflux...

... share metabolic pathways, we measured the effects of GGH overexpression on folic acid metabolism. The full-length cDNA for GGH, subcloned into a constitutive expression *vector*, was transfected into a human fibrosarcoma (HT-1080) and a human breast carcinoma (MCF-7) cell line. Compared with the clones containing an empty *vector*, the GGH-overexpressing cells express 15- to 30-fold more GGH mRNA, more GGH protein, and 15- to 90-fold more GGH enzyme activity. GGH...
Descriptors: Antimetabolites, Antineoplastic--metabolism--ME; *Antimetabolites, Antineoplastic--pharmacology--PD; **Methotrexate*--metabolism--ME; **Methotrexate*--pharmacology--PD; *gamma-Glutamyl Hydrolase--biosynthesis--BI...; pharmacokinetics--PK; Breast Neoplasms--drug therapy--DT; Breast Neoplasms--enzymology--EN; Drug Resistance, Neoplasm; Fibrosarcoma--drug therapy--DT; Fibrosarcoma--enzymology--EN; Folic Acid--physiology--PH; *Methotrexate*--pharmacokinetics--PK; RNA, Messenger--biosynthesis--BI; RNA, Messenger--genetics--GE; Reverse Transcriptase Polymerase Chain Reaction; Tetrahydrofolates--pharmacokinetics--PK; Transfection; *Tumor* Cells, Cultured; gamma-Glutamyl Hydrolase--genetics--GE
Chemical Name: Antimetabolites, Antineoplastic; RNA, Messenger; Tetrahydrofolates; 5-methyltetrahydrofolate; *Methotrexate*; Folic Acid; gamma-Glutamyl Hydrolase

11/3,K/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10806665 99341974 PMID: 10413425
***Folylpolyglutamyl* *synthetase* gene transfer and glioma *antifolate* sensitivity in culture and in vivo.**
Aghi M; Kramm CM; Breakefield XO
Department of Neurology, Massachusetts General Hospital, Boston, MA, USA.
Journal of the National Cancer Institute (UNITED STATES) Jul 21 1999, 91 (14) p1233-41, ISSN 0027-8874 Journal Code: J9J
Contract/Grant No.: P30CA69246, CA, NCI
Comment in J Natl Cancer Inst. 1999 Dec 1;91(23) 2047-50; Comment in J Natl Cancer Inst. 1999 Jul 21;91(14):1178-9
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Folylpolyglutamyl* *synthetase* gene transfer and glioma *antifolate

sensitivity in culture and in vivo.
... against slow-growing tumors and are toxic to actively replicating cells in normal tissues. These drugs are converted intracellularly into polyglutamate derivatives by the enzyme *folylpolyglutamyl* *synthetase* (*FPGS*). Because tumors with high expression of *FPGS* often respond to nontoxic *antifolate* doses, we investigated whether augmenting tumoral *FPGS* activity by gene delivery would enhance tumoral *antifolate* sensitivity. METHODS: 9L rat gliosarcoma cells were stably transfected with a human *FPGS* complementary DNA (cDNA), producing 9L/*FPGS* cells. The sensitivity of these cells to the antifolates *methotrexate* and *edatrexate* was measured in culture and in subcutaneous tumors, as was their ability to increase the chemosensitivity of nearby nontransfected cells, i.e., a bystander effect. The *antifolate* sensitivity of nonselected cells transduced with a hybrid amplicon *vector* that expressed *FPGS* was also ascertained. RESULTS: In comparison with 9L cells, 9L/ *FPGS* cells displayed enhanced sensitivity to 4-hour pulses of *antifolate*. Subcutaneous 9L/*FPGS* tumors responded as well to *methotrexate* given every third day as 9L tumors did to daily treatment. A modest bystander effect was observed with *edatrexate* treatment in culture and in vivo. The observed bystander effect appeared to result from the release of antifolates by transfected cells after the removal of extracellular drug. In culture, enhanced *antifolate* sensitivity was also seen in other stably transfected rodent and human glioma cell lines, including one with high pre-existing *FPGS* activity, and in canine and human glioblastoma cell lines transduced with a *vector* bearing *FPGS* cDNA. CONCLUSIONS: *FPGS* gene delivery enhances the *antifolate* sensitivity of several glioma cell lines and merits further evaluation as a therapeutic strategy.
Descriptors: *Aminopterin*--analogs and derivatives--AA; *Antimetabolites, Antineoplastic--pharmacology--PD; *Folic Acid Antagonists--pharmacology --PD; *Gene Therapy--methods--MT; *Gene Transfer Techniques; * *Methotrexate*--pharmacology--PD; *Neoplasms--therapy--TH; *Peptide Synthases--genetics--GE; *Aminopterin*--pharmacology--PD; Chromatography, Thin Layer; Dogs; Dose-Response Relationship, Drug; Glioma; Neoplasms --enzymology--EN; Neoplasms--genetics--GE; Peptide Synthases--metabolism --ME; Rats; Transduction, Genetic; Transfection; *Tumor* Cells, Cultured
Chemical Name: Antimetabolites, Antineoplastic; Folic Acid Antagonists; *Aminopterin*; *Methotrexate*; *edatrexate*; Peptide Synthases; folylpolyglutamate synthetase
?ds

Set	Items	Description
S1	609	(FPGS OR (FOLYLPOLYGLUTAMYL (W) SYNTHETASE))
S2	13	S1 AND REVIEW
S3	11	RD (unique items)
S4	195	S1 AND (GENE OR CDNA OR DNA)
S5	1	S4 AND REVIEW
S6	61	S4 AND (MAMMAL OR ANIMAL)
S7	35	RD (unique items)
S8	355	S1 AND (CANCER OR (NEOPLATIC (W) CELL) OR TUMOR OR TUMOUR)
S9	233	S8 AND (ANTIFOLATE OR METHOTREXATE OR EDATREXATE OR AMINOP-TERIN OR (THYMIDYLATE (W) SYNTHETASE (W) INHIBITOR))
S10	6	S9 AND (VECTOR)
S11	2	RD (unique items)

?s s9 and (gene (w) delivery)

	233	S9
	1856966	GENE
	324865	DELIVERY
	7440	GENE(W)DELIVERY
S12	4	S9 AND (GENE (W) DELIVERY)

?rd
...completed examining records

S13	1	RD (unique items)

?t s13/3,k/all

13/3,K/1 (Item 1 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

10806665 99341974 PMID: 10413425

***Folylpolyglutamyl* *synthetase* gene transfer and glioma *antifolate* sensitivity in culture and in vivo.**

Aghi M; Kramm CM; Breakefield XO

Department of Neurology, Massachusetts General Hospital, Boston, MA, USA.

Journal of the National Cancer Institute (UNITED STATES) Jul 21 1999, 91 (14) p1233-41, ISSN 0027-8874 Journal Code: J9J

Contract/Grant No.: P30CA69246, CA, NCI

Comment in J Natl Cancer Inst. 1999 Dec 1;91(23) 2047-50; Comment in J Natl Cancer Inst. 1999 Jul 21;91(14):1178-9

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

***Folylpolyglutamyl* *synthetase* gene transfer and glioma *antifolate* sensitivity in culture and in vivo.**

... against slow-growing tumors and are toxic to actively replicating cells in normal tissues. These drugs are converted intracellularly into polyglutamate derivatives by the enzyme *folylpolyglutamyl* *synthetase* (*FPGS*). Because tumors with high expression of *FPGS* often respond to nontoxic *antifolate* doses, we investigated whether augmenting tumoral *FPGS* activity by *gene* *delivery* would enhance tumoral *antifolate* sensitivity. METHODS: 9L rat gliosarcoma cells were stably transfected with a human *FPGS* complementary DNA (cDNA), producing 9L/*FPGS* cells. The sensitivity of these cells to the antifolates *methotrexate* and *edatrexate* was measured in culture and in subcutaneous tumors, as was their ability to increase the chemosensitivity of nearby nontransfected cells, i.e., a bystander effect. The *antifolate* sensitivity of nonselected cells transduced with a hybrid amplicon vector that expressed *FPGS* was also ascertained. RESULTS: In comparison with 9L cells, 9L/ *FPGS* cells displayed enhanced sensitivity to 4-hour pulses of *antifolate*. Subcutaneous 9L/*FPGS* tumors responded as well to *methotrexate* given every third day as 9L tumors did to daily treatment. A modest bystander effect was observed with *edatrexate* treatment in culture and in vivo. The observed bystander effect appeared to result from the release of antifolates by transfected cells after the removal of extracellular drug. In culture, enhanced *antifolate* sensitivity was also seen in other stably transfected rodent and human glioma cell lines, including one with high pre-existing *FPGS* activity, and in canine and human glioblastoma cell lines transduced with a vector bearing *FPGS* cDNA. CONCLUSIONS: *FPGS* *gene* *delivery* enhances the *antifolate* sensitivity of several glioma cell lines and merits further evaluation as a therapeutic strategy.

Descriptors: *Aminopterin*--analogs and derivatives--AA; *Antimetabolites, Antineoplastic--pharmacology--PD; *Folic Acid Antagonists--pharmacology --PD; *Gene Therapy--methods--MT; *Gene Transfer Techniques; * *Methotrexate*--pharmacology--PD; *Neoplasms--therapy--TH; *Peptide Synthases--genetics--GE; *Aminopterin*--pharmacology--PD; Chromatography, Thin Layer; Dogs; Dose-Response Relationship, Drug; Glioma; Neoplasms --enzymology--EN; Neoplasms--genetics--GE; Peptide Synthases--metabolism --ME; Rats; Transduction, Genetic; Transfection; *Tumor* Cells, Cultured

Chemical Name: Antimetabolites, Antineoplastic; Folic Acid Antagonists; *Aminopterin*; *Methotrexate*; *edatrexate*; Peptide Synthases; folylpolyglutamate synthetase

?ds

Set	Items	Description
S1	609	(FPGS OR (FOLYLPOLYGLUTAMYL (W) SYNTHETASE))
S2	13	S1 AND REVIEW
S3	11	RD (unique items)
S4	195	S1 AND (GENE OR CDNA OR DNA)
S5	1	S4 AND REVIEW
S6	61	S4 AND (MAMMAL OR ANIMAL)
S7	35	RD (unique items)

```
S8         355   S1 AND (CANCER OR (NEOPLATIC (W) CELL) OR TUMOR OR TUMOUR)
S9         233   S8 AND (ANTIFOLATE OR METHOTREXATE OR EDATREXATE OR AMINOP-
              TERIN OR (THYMIDYLATE (W) SYNTHETASE (W) INHIBITOR))
S10          6   S9 AND (VECTOR)
S11          2   RD (unique items)
S12          4   S9 AND (GENE (W) DELIVERY)
S13          1   RD (unique items)
?s s9 and (gene (w) (therapy or treatment))
Processing
             233  S9
         1856966  GENE
         4555207  THERAPY
         3919672  TREATMENT
           54900  GENE(W)(THERAPY OR TREATMENT)
     S14       8  S9 AND (GENE (W) (THERAPY OR TREATMENT))
?rd
...completed examining records
     S15       3  RD (unique items)
?t s15/3,k/all

 15/3,K/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10806665   99341974   PMID: 10413425
  *Folylpolyglutamyl* *synthetase* gene transfer and glioma *antifolate*
 sensitivity in culture and in vivo.
  Aghi M; Kramm CM; Breakefield XO
  Department of Neurology, Massachusetts General Hospital, Boston, MA, USA.
  Journal of the National Cancer Institute (UNITED STATES)   Jul 21 1999,
91  (14)  p1233-41,  ISSN 0027-8874   Journal Code: J9J
  Contract/Grant No.: P30CA69246, CA, NCI
  Comment  in J  Natl  Cancer Inst. 1999 Dec 1;91(23) 2047-50; Comment in J
Natl Cancer Inst. 1999 Jul 21;91(14):1178-9
  Languages: ENGLISH
  Document type: Journal Article
  Record type: Completed

  *Folylpolyglutamyl* *synthetase* gene transfer and glioma *antifolate*
 sensitivity in culture and in vivo.
  ... against slow-growing tumors and are toxic to actively replicating
cells in normal tissues. These drugs are converted intracellularly into
polyglutamate derivatives by the enzyme *folylpolyglutamyl* *synthetase* (
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sensitivity. METHODS: 9L rat gliosarcoma cells were stably transfected with
a human *FPGS* complementary DNA (cDNA), producing 9L/*FPGS* cells. The
sensitivity of these cells to the antifolates *methotrexate* and
*edatrexate* was measured in culture and in subcutaneous tumors, as was
their ability to increase the chemosensitivity of nearby nontransfected
cells, i.e., a bystander effect. The *antifolate* sensitivity of
nonselected cells transduced with a hybrid amplicon vector that expressed
*FPGS* was also ascertained. RESULTS: In comparison with 9L cells, 9L/
*FPGS* cells displayed enhanced sensitivity to 4-hour pulses of
*antifolate*. Subcutaneous 9L/*FPGS* tumors responded as well to
*methotrexate* given every third day as 9L tumors did to daily treatment. A
modest bystander effect was observed with *edatrexate* treatment in culture
and in vivo. The observed bystander effect appeared to result from the
release of antifolates by transfected cells after the removal of
extracellular drug. In culture, enhanced *antifolate* sensitivity was also
seen in other stably transfected rodent and human glioma cell lines,
including one with high pre-existing *FPGS* activity, and in canine and
human glioblastoma cell lines transduced with a vector bearing *FPGS* cDNA.
CONCLUSIONS: *FPGS* gene delivery enhances the *antifolate* sensitivity of
several glioma cell lines and merits further evaluation as a therapeutic
strategy.
```

Descriptors: *Aminopterin*--analogs and derivatives--AA; *Antimetabolites, Antineoplastic--pharmacology--PD; *Folic Acid Antagonists--pharmacology --PD; **Gene* *Therapy*--methods--MT; *Gene Transfer Techniques; * *Methotrexate*--pharmacology--PD; *Neoplasms--therapy--TH; *Peptide Synthases--genetics--GE; *Aminopterin*--pharmacology--PD; Chromatography, Thin Layer; Dogs; Dose-Response Relationship, Drug; Glioma; Neoplasms --enzymology--EN; Neoplasms--genetics--GE; Peptide Synthases--metabolism --ME; Rats; Transduction, Genetic; Transfection; *Tumor* Cells, Cultured

Chemical Name: Antimetabolites, Antineoplastic; Folic Acid Antagonists; *Aminopterin*; *Methotrexate*; *edatrexate*; Peptide Synthases; folylpolyglutamate synthetase

15/3,K/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10770844 20048020 PMID: 10580033

Re: *Folylpolyglutamyl* *synthetase* gene transfer and glioma *antifolate* sensitivity in culture and in vivo.

Jansen G; Peters GJ; Pinedo HM; Priest DG; Assaraf YG

Journal of the National Cancer Institute (UNITED STATES) Dec 1 1999, 91 (23) p2047-50, ISSN 0027-8874 Journal Code: J9J

Comment on J Natl Cancer Inst. 1999 Jul 21;91(14) 1178-9; Comment on J Natl Cancer Inst. 1999 Jul 21;91(14):1233-41

Languages: ENGLISH

Document type: Comment; Letter

Record type: Completed

Re: *Folylpolyglutamyl* *synthetase* gene transfer and glioma *antifolate* sensitivity in culture and in vivo.

Descriptors: Antimetabolites, Antineoplastic--therapeutic use--TU; *Enzyme Inhibitors--therapeutic use--TU; *Folic Acid Antagonists --therapeutic use--TU; **Gene* *Therapy*; *Glioma--therapy--TH; *Peptide Synthases--genetics--GE; Gene Transfer Techniques; Glioma--enzymology--EN; *Tumor* Cells, Cultured

15/3,K/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09670296 98140502 PMID: 9479873

Cellular and molecular mechanisms of resistance to *antifolate* drugs: new analogues and approaches to overcome the resistance.

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International journal of hematology (IRELAND) Dec 1997, 66 (4) p459-77, ISSN 0925-5710 Journal Code: A7F

Erratum in Int J Hematol 1998 Apr;67(3) 333

Languages: ENGLISH

Document type: Journal Article; Review; Review, Academic

Record type: Completed

Cellular and molecular mechanisms of resistance to *antifolate* drugs: new analogues and approaches to overcome the resistance.

A number of *antifolate* drugs, which inhibit the key enzymes in the 'thymidylate cycle', dihydrofolate reductase (DHFR) and thymidylate synthase (TS), have been developed as part of the search for analogues with superior antitumor efficacy to a 'classical' *antifolate*, *methotrexate* (MTX), and those which are active against the MTX-resistant *tumor* cells. Recent development of newer classes of *antifolate* drugs is based on the extensive understanding of the relationship between chemical structures and biological properties and of analogue interactions with target enzymes, transport proteins and folate metabolizing enzyme, folylpolyglutamate synthetase (*FPGS*). *Tumor* cells may develop resistance to an *antifolate* drug by virtue of, (1) amplified activity in its target

enzyme, (2) impaired function of drug transport protein, e.g. reduced folate carrier (RFC), (3) induction of mutated target enzyme with low affinity for *antifolate*(s), and (4) defective polyglutamation of drug(s) in the cells. Recent studies have elucidated in part the molecular events involved in the resistance to...

... include amplification and/or mutation of the gene encoding a target enzyme, reduced or altered gene expression of the RFC, and mutated expression of the *FPGS* gene. To overcome or circumvent the resistance mechanisms, new antifolates with diverse structures and different biological properties have been designed and developed for clinical use. Trimetrexate (TMQ), a lipophilic DHFR inhibitor which is not a substrate for RFC and *FPGS*, could overcome the MTX-resistance through impaired RFC and diminished polyglutamation, and partially through amplified DHFR. Selective inhibitors of TS with a folate structure such as raltitrexed could circumvent the resistance by virtue of DHFR overproduction, and this class of compounds which have higher substrate activities for *FPGS* than MTX may be of value for the treatment of myeloid leukemias in addition to lymphocytic malignancies resistant to conventional chemotherapy. Several strategies to overcome *antifolate* resistance by using *gene* *therapy* are currently under investigation.
; Drug Resistance--physiology--PH; Leukemia--pathology--PA; *Tumor* Cells, Cultured
?ds

Set	Items	Description
S1	609	(FPGS OR (FOLYLPOLYGLUTAMYL (W) SYNTHETASE))
S2	13	S1 AND REVIEW
S3	11	RD (unique items)
S4	195	S1 AND (GENE OR CDNA OR DNA)
S5	1	S4 AND REVIEW
S6	61	S4 AND (MAMMAL OR ANIMAL)
S7	35	RD (unique items)
S8	355	S1 AND (CANCER OR (NEOPLATIC (W) CELL) OR TUMOR OR TUMOUR)
S9	233	S8 AND (ANTIFOLATE OR METHOTREXATE OR EDATREXATE OR AMINOPTERIN OR (THYMIDYLATE (W) SYNTHETASE (W) INHIBITOR))
S10	6	S9 AND (VECTOR)
S11	2	RD (unique items)
S12	4	S9 AND (GENE (W) DELIVERY)
S13	1	RD (unique items)
S14	8	S9 AND (GENE (W) (THERAPY OR TREATMENT))
S15	3	RD (unique items)

?s s9 and (gene (w) transfer)

	233	S9
	1856966	GENE
	454121	TRANSFER
	50609	GENE(W)TRANSFER
S16	7	S9 AND (GENE (W) TRANSFER)

?rd
...completed examining records

S17	2	RD (unique items)

?t s17/3,k/all

17/3,K/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10806665 99341974 PMID: 10413425
***Folylpolyglutamyl* *synthetase* *gene* *transfer* and glioma *antifolate* sensitivity in culture and in vivo.**
Aghi M; Kramm CM; Breakefield XO
Department of Neurology, Massachusetts General Hospital, Boston, MA, USA.
Journal of the National Cancer Institute (UNITED STATES) Jul 21 1999, 91 (14) p1233-41, ISSN 0027-8874 Journal Code: J9J
Contract/Grant No.: P30CA69246, CA, NCI
Comment in J Natl Cancer Inst. 1999 Dec 1;91(23) 2047-50; Comment in J Natl Cancer Inst. 1999 Jul 21;91(14):1178-9

Languages: ENGLISH
Document type: Journal Article
Record type: Completed

***Folylpolyglutamyl* *synthetase* *gene* *transfer* and glioma *antifolate* sensitivity in culture and in vivo.**

... against slow-growing tumors and are toxic to actively replicating cells in normal tissues. These drugs are converted intracellularly into polyglutamate derivatives by the enzyme *folylpolyglutamyl* *synthetase* (*FPGS*). Because tumors with high expression of *FPGS* often respond to nontoxic *antifolate* doses, we investigated whether augmenting tumoral *FPGS* activity by gene delivery would enhance tumoral *antifolate* sensitivity. METHODS: 9L rat gliosarcoma cells were stably transfected with a human *FPGS* complementary DNA (cDNA), producing 9L/*FPGS* cells. The sensitivity of these cells to the antifolates *methotrexate* and *edatrexate* was measured in culture and in subcutaneous tumors, as was their ability to increase the chemosensitivity of nearby nontransfected cells, i.e., a bystander effect. The *antifolate* sensitivity of nonselected cells transduced with a hybrid amplicon vector that expressed *FPGS* was also ascertained. RESULTS: In comparison with 9L cells, 9L/ *FPGS* cells displayed enhanced sensitivity to 4-hour pulses of *antifolate*. Subcutaneous 9L/*FPGS* tumors responded as well to *methotrexate* given every third day as 9L tumors did to daily treatment. A modest bystander effect was observed with *edatrexate* treatment in culture and in vivo. The observed bystander effect appeared to result from the release of antifolates by transfected cells after the removal of extracellular drug. In culture, enhanced *antifolate* sensitivity was also seen in other stably transfected rodent and human glioma cell lines, including one with high pre-existing *FPGS* activity, and in canine and human glioblastoma cell lines transduced with a vector bearing *FPGS* cDNA. CONCLUSIONS: *FPGS* gene delivery enhances the *antifolate* sensitivity of several glioma cell lines and merits further evaluation as a therapeutic strategy.

Descriptors: *Aminopterin*--analogs and derivatives--AA; *Antimetabolites, Antineoplastic--pharmacology--PD; *Folic Acid Antagonists--pharmacology --PD; *Gene Therapy--methods--MT; **Gene* *Transfer* Techniques; * *Methotrexate*--pharmacology--PD; *Neoplasms--therapy--TH; *Peptide Synthases--genetics--GE; *Aminopterin*--pharmacology--PD; Chromatography, Thin Layer; Dogs; Dose-Response Relationship, Drug; Glioma; Neoplasms --enzymology--EN; Neoplasms--genetics--GE; Peptide Synthases--metabolism --ME; Rats; Transduction, Genetic; Transfection; *Tumor* Cells, Cultured

Chemical Name: Antimetabolites, Antineoplastic; Folic Acid Antagonists; *Aminopterin*; *Methotrexate*; *edatrexate*; Peptide Synthases; folylpolyglutamate synthetase

17/3,K/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10770844 20048020 PMID: 10580033

Re: *Folylpolyglutamyl* *synthetase* *gene* *transfer* and glioma *antifolate* sensitivity in culture and in vivo.

Jansen G; Peters GJ; Pinedo HM; Priest DG; Assaraf YG

Journal of the National Cancer Institute (UNITED STATES) Dec 1 1999, 91 (23) p2047-50, ISSN 0027-8874 Journal Code: J9J

Comment on J Natl Cancer Inst. 1999 Jul 21;91(14) 1178-9; Comment on J Natl Cancer Inst. 1999 Jul 21;91(14):1233-41

Languages: ENGLISH
Document type: Comment; Letter
Record type: Completed

Re: *Folylpolyglutamyl* *synthetase* *gene* *transfer* and glioma *antifolate* sensitivity in culture and in vivo.

; *Gene* *Transfer* Techniques; Glioma--enzymology--EN; *Tumor* Cells, Cultured

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